An investigation of the interrelationships between multibehaviours and multimorbidity

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Abstract

This thesis addresses the complex interplay between multimorbidity and multibehaviours at theoretical and practical levels. Grounded primarily in pragmatic philosophy and influenced by the interpretive turn of postmodernism, this thesis adopted a mixed-method methodology. The primary aim was twofold: to establish a scientifically supported association between multimorbidity and multibehaviours to inform the development of future guidelines; to enhance our understanding of patient-centred care, focusing on the combined impact of multimorbidity and multibehaviours on the relationship between healthcare providers and people with multimorbidity.

These aims were addressed through four main studies. First, a systematic review and meta-analysis provided novel evidence by quantifying the dose-response association between various types of combined and accumulative SNAP health risk behaviours and multimorbidity using various operational definitions for multimorbidity (MM2+ and MM3+).

Second, an epidemiological study of electronic health records for 21,079 adults in Staffordshire corroborated these findings and extended the research to encompass complex multimorbidity (three or more conditions affecting at least three different organ systems), and stricter cutoff points. Analyses also identified interchangeable sex-specific patterns that varied with definition of multimorbidity applied and with the number of SNAP health risk behaviours. This underscored both the clinical significance of the identified outcomes for promoting tailored multimorbidity guidelines and the need for further sex-sensitive research.

Third, factorial analysis of electronic health record data focused on the 7,560 adults with multimorbidity who engaged with multiple lifestyle behaviours that pose a health risk (‘multibehaviours’). Again, differential patterns of associative multimorbidity emerged, indicating statistical clustering of multimorbidities in people who have engaged with multibehaviours. However, only a cardiovascular pattern commonly emerged in both sexes, further highlighting the importance of sex differences in this area.

The final study examined the novel application of a qualitative methodology, Situational Analysis, to explore the combined impact of multimorbidity-multibehaviours on the

healing relationship. This addressed a significant gap in the literature, contributing to a deeper understanding of adequate healthcare provision for people with multimorbidity under the conceptual framework of the salutogenesis-iatrogenesis dipole.

In summary, the thesis scrutinised the complex dynamics of multimorbidity and multibehaviours, advocating for the integration of behavioural change theories into multimorbidity care. Recognising the importance of addressing health risk behaviours and the evolving needs of postmodern patients, healthcare providers can tailor interventions to enhance patient outcomes effectively. Efforts to reform healthcare systems should prioritise a person-centred care shift in multimorbidity management toward a more salutogenic approach in order the specific health phenomenon to be address comprehensively. Central to this is the incorporation of behavioural change strategies as a counterbalance factor against current medicalisation of multimorbidity management.

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List of Acronyms

≥12CC – represents the inclusion of twelve or more morbidities in multimorbidity measurement, providing a comprehensive assessment of health conditions within an individual

2+CM – signifies the presence of two or more comorbidities within an individual.

MCC – stands for the occurrence of multiple chronic conditions within a single individual.

ACG - Adjusted Clinical Groups is a classification system used to evaluate patterns of healthcare utilization and predict future healthcare needs based on patients' clinical characteristics and health status.

ADL- ADL, short for Activities of Daily Living, encompasses the essential tasks individuals typically perform in their daily lives, such as bathing, dressing, eating, and mobility, serving as a measure of functional independence and overall well-being, particularly in the context of healthcare and eldercare assessments.

AF - Atrial fibrillation is a heart rhythm disorder characterized by rapid and irregular electrical activity in the atria, leading to an increased risk of blood clots, stroke, and other cardiovascular complications.

CDS - stands for Chronic Disease Score, a tool used to quantify the burden of chronic diseases in individuals or populations for research or clinical purposes.

CHD - stands for Coronary Heart Disease, a condition where plaque builds up inside the coronary arteries, leading to reduced blood flow to the heart muscle, which can result in chest pain (angina) or heart attack.

CIRS – Cumulative Illness Rating Scale s a tool utilized by healthcare professionals to assess the overall burden of illness in patients by scoring various medical conditions across different organ systems.

CKD - stands for Chronic Kidney Disease, a condition characterized by the gradual loss of kidney function over time, often leading to complications such as fluid retention, electrolyte imbalances, and cardiovascular disease.

CLD - Chronic liver disease (CLD) refers to a progressive condition characterized by long-term damage to the liver, often caused by factors such as alcohol consumption, viral infections, or metabolic disorders, leading to impaired liver function and potentially serious complications over time.

COPD - stands for Chronic Obstructive Pulmonary Disease, a progressive lung disease characterized by airflow limitation and breathing difficulties, often caused by long-term exposure to irritants such as cigarette smoke.

CSU - The Commissioning Support Unit (CSU) in the NHS provides specialized expertise and support services to clinical commissioning groups (CCGs) and other healthcare organizations to help them effectively plan, procure, and deliver high-quality healthcare services for their local populations.

DUSOI - refers to the Duke Severity of Illness Checklist, a validated tool used to assess the severity of illness in hospitalized patients based on various clinical parameters.

EHR - Electronic health records) are digital versions of patients' medical histories, containing comprehensive information about their health status, treatments, medications, test results, and

other relevant data, accessible to authorized healthcare providers for efficient and coordinated patient care.

EMIS -web EMIS Web is a clinical information system widely used in healthcare settings, providing electronic medical records management, patient scheduling, and other essential tools to support healthcare professionals in delivering efficient and effective patient care.

EPOC - stands for Effective Practice and Organisation of Care, a group within the Cochrane Collaboration that focuses on producing systematic reviews of interventions aimed at improving health system performance and organization.

GPs- General practitioners (GPs) are primary care physicians who serve as the first point of contact for patients seeking medical care, offering a wide range of healthcare services, including diagnosis, treatment, preventive care, and referrals to specialists when needed, within the framework of general practice settings

GRADE - The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach provides a structured framework for evaluating the quality of evidence from systematic reviews and meta-analyses, enhancing transparency and reliability in synthesizing research findings for clinical decision-making.

HR- stands for hazard ratio, a statistical measure used to assess the relative risk of an event occurring over time in different groups, typically in survival analysis studies

HRQOL – stands for Health-Related Quality of Life, a multidimensional concept that encompasses physical, mental, emotional, and social aspects of well-being as they relate to health and illness.

IBD - Inflammatory bowel disease (IBD) encompasses a group of chronic inflammatory conditions of the gastrointestinal tract, including Crohn's disease and ulcerative colitis, which can cause symptoms such as abdominal pain, diarrhoea, and inflammation, requiring ongoing management and treatment to control flare-ups and maintain quality of life.

IBS - Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by abdominal pain, bloating, and changes in bowel habits, without any evidence of underlying structural abnormalities.

LSOA - Layer Super Output Areas (LSOAs) are geographic units used in the United Kingdom for reporting small area statistics, allowing for the analysis of socio-economic and demographic data at a granular level to support research, policy development, and resource allocation.

MCC12- multiple chronic conditions 12 - derived from a specific study, denotes the examination of twelve major co-existing morbidities within participants, shedding light on the complex interplay of health conditions and informing targeted interventions to improve overall health outcomes.

MCC8 - denotes the examination of eight primary morbidities that co-occur in diverse manifestations among participants of the particular study

MeSH - stands for Medical Subject Headings, a controlled vocabulary thesaurus used for indexing articles in the National Library of Medicine's PubMed database, facilitating precise and efficient literature searches

MM- refers to the phenomenon of multimorbidity, which involves the acquisition of two or more related and/or unrelated chronic conditions within an individual.

MM2+ - is an operational definition for multimorbidity, indicating the acquisition of two or more morbidities within the same individual.

MM3+ - serves as an operational definition for multimorbidity, specifically denoting the acquisition of three or more morbidities within the same individual.

MS- refers to the specific chronic condition of Multiple Sclerosis, a neurological disorder affecting the central nervous system.

NCD- Non-Communicable Disease, serves as an umbrella term for chronic health conditions

NHS - The National Health Service (NHS) is the publicly funded healthcare system in the United Kingdom, providing comprehensive medical services to residents regardless of their ability to pay at the point of use.

OAs - Output Areas (OAs) are small geographic units used in the United Kingdom for reporting census and other statistical data, providing a fine-grained spatial framework for analyzing population characteristics and socio-economic trends within local communities.

OR- stands for odds ratio, a statistical measure used to quantify the strength and direction of the association between two variables in a case-control study.

PAF - Principal Axis Factoring (PAF) is a statistical technique used in factor analysis to identify underlying patterns or factors within a dataset, particularly in the social sciences, by extracting common variance shared among variables while minimizing error variance. KMO- Kaiser-Mayer-Olkin measure.

PVD - stands for Peripheral Vascular Disease, a condition characterized by the narrowing or blockage of blood vessels outside of the heart and brain, often leading to reduced blood flow to the extremities.

QOF - stands for Quality and Outcomes Framework, a system in the United Kingdom that rewards general practices for the provision of quality care and achieving specific clinical targets.

RF- stands for "risk factor," indicating variables or conditions that increase the likelihood of developing a particular disease or experiencing a health issue

ROBINS-E - stands for Risk of Bias in Non-randomized Studies - of Exposures, an assessment tool used to evaluate the risk of bias in non-randomized studies of exposures.

ROBINS-I - (Risk Of Bias In Non-randomized Studies - of Interventions) is a tool specifically designed to assess the risk of bias in non-randomized studies included in systematic reviews, helping researchers and clinicians evaluate the quality and reliability of evidence derived from observational studies.

SNAP - stands for smoking, nutrition, alcohol, and physical activity, collectively representing key lifestyle factors that influence health outcomes.

SPSS - SPSS (Statistical Package for the Social Sciences) is a widely-used software tool for statistical analysis and data management, offering a range of features for researchers, analysts, and students to explore, visualize, and interpret data from various sources.

Stroke TIA - A transient ischemic attack (TIA), often referred to as a "mini-stroke," is a temporary episode of neurological dysfunction caused by a brief interruption in blood flow to the brain, typically lasting less than 24 hours, and often serving as a warning sign for a potential future stroke.

1. Introduction and literature review

1.1 Introduction: the multimorbid-multibehaviours joint inquiry

In recent years, there has been a gradual conceptual shift in the theoretical landscape of healthcare. This acknowledges that health phenomena, including morbidities and health risk behaviours such as smoking, nutrition, alcohol intake, and physical activity, exhibit multiple properties rather than singular ones. This evolution has led to the emergence of concepts such as multimorbidity (multiple or more concurrent chronic conditions) and multibehaviours (engaging in multiple or more health risk behaviours), which have garnered significant attention in both curative and preventive medicine, respectively.

Figures in the scientific community, such as Prochaska (2008) and Loprinzi (2015), have advocated for a shift in the current healthcare system to incorporate ideas from both behavioural and clinical paradigms. They propose breaking down disciplinary silos and fostering interdisciplinary collaboration under a unified multimorbidity-multibehaviours theoretical and clinical framework. This approach aims to transform the existing monomorbid healthcare system, promoting more effective person-centred care compared to the current medicalised, disease-based approach.

Several methodological challenges, primarily stemming from the complex and elusive nature of multimorbidity, obscure and complicate our understanding of this phenomenon (Sinnige et al. 2013), which must be addressed in the current project. Perhaps the most perplexing issue in multimorbidity research pertains to the lack of a standardised definition and measurement approach, leading to numerous subjective decisions (Weis et al 2014). Two systematic reviews have recommended that the choice of a measure should be guided by the specific outcome of interest and the type of available data (Diederich et al. 2011; Huntley et al. 2012). A third systematic review (Fortin et al. 2012) suggested incorporating all possible operational definitions into analyses.

To gain a deeper understanding, the methodological inquiry into multimorbidity presented in this thesis can be divided into three main domains, focusing on how to define and measure this phenomenon specifically. The first domain concerns the etiological investigation of the association of multibehaviours with multimorbidity risk.

Methodological challenges arise regarding how many morbidities should be included within the operational definition, what types of morbidities (e.g., disorders, risk factors, or symptoms), and which cut-offs (e.g., MM2+, MM3+) or cumulative indices are best suited to capture both the clinical objectivity and the personal impact of the association under investigation.

The second domain involves the scientific community's shift towards data-driven methods. During this phase, advanced statistical techniques such as cluster analysis and exploratory factor analysis were employed on specific datasets to identify causal associations between morbidities. This approach offered clinically valuable insights into how interventions can be targeted (Prados-Torres et al., 2012).

In the third domain of multimorbidity definition, a more novel and contemporary approach emerged. Instead of proposing another reductionist biomedical framework that focuses on physical, this approach advocates that we embrace multimorbidity as an experiential outcome for those affected. It acknowledges that their experiences are shaped by the gap between medical policy and their lived realities as they navigate the healthcare system and treatment processes (Blarikom et al. 2023).

To contribute to this overarching goal, the present thesis investigates the interrelationship between multimorbidity and multibehaviours at theoretical and practical levels within healthcare settings. By adopting a holistic approach, this series of studies addresses key issues that contribute to the development of a comprehensive joint multimorbidity-multibehaviours framework.

The following sections consider the relevant literature before setting out the thesis aims and objectives, and how the thesis is structured to address them.

1.2 Historical origins of multimorbidity

Over the past fifty years, epidemiological studies have revealed the increasing number of individuals affected by multiple concurrent chronic conditions. This phenomenon has gradually emerged as a significant public health concern. It has been estimated that approximately 14.2 to 15.4 million adults in England are affected by multiple chronic conditions(Bower et al. 2011; Göpfert et al. 2020). Currently, surveillance systems in the UK have shown prevalence rates of the adult population now experiencing

multimorbidity to balance between 23 -27% (Pearson-Stuttard et al. 2019; Göpfert et al. 2020). Projected estimations, furthermore, reveal a concerning picture, showing a negative trend with approximately two-thirds of individuals aged 65 and over in England experiencing multi-morbidity by 2035, with 17% of the UK population expected to suffer from four or more chronic conditions by 2035. This projection nearly doubles the current prevalence rate of 9.8% (Pearson-Stuttard et al, 2019; Lyons et al., 2021).

The exploration of individuals with multiple chronic conditions began with the implementation of the Cumulative Illness Rating Scale by Linn et al. (1968), which laid the groundwork for the introduction of the term "comorbidity" by Feinstein (1970). This terminology denoted the presence of additional peripheral health entities alongside a primary or “index” chronic disease (Salive, 2013). However, the sole focus on the index condition gave impetus to the emergence of the multimorbidity construct, which underscores the limitations of the comorbidity concept in addressing the holistic needs of individuals and perpetuates a single-disease mentality. Shifting attention away from the index condition, multimorbidity emphasises the equal importance of acquired chronic conditions (Buffel du Vaure et al. 2016) and prioritises the personhood of the individual over the disease, thereby introducing a biopsychosocial perspective to the management of multiple chronic conditions (Skou et al. 2022).

Despite being distinct, comorbidity and multimorbidity are often used interchangeably in the literature (Buffel du Vaure et al., 2016), leading to understandable confusion regarding their usage (Fortin et al., 2004), even within healthcare settings (further elaborated in Chapter 6).

1.3 Impact and consequences of multimorbidity

The impact of multimorbidity expands from the personal to the systemic level, influencing the operation of the healthcare system.

1.3.1 Personal impact of multimorbidity

Consistent epidemiological evidence indicates that multimorbidity significantly impacts the personal life of those affected in multiple ways. It can reduce people’s well-being (Luben et al. 2020), increase their risk for premature death (Mounce et al. 2018) and

augments vulnerability toward adverse health outcomes and acute conditions (Cheryl et al. 2014). This was clear through the greater vulnerabilities of those with chronic conditions to infection and more severe symptoms during the COVID-19 pandemic (Skou et al. 2022). Furthermore, the multimorbidity entails burdensome management requirements (Bratzke et al. 2015), which links to high healthcare utilisation and costs and impaired quality of life (Marengoni et al. 2011).

Fortin et al. (2004) demonstrated that while multimorbidity could impact various aspects of health-related quality of life (HRQoL), its effects on psychological and social dimensions were less pronounced than for physical domains. Ryan et al.'s (2015) systematic review highlighted one of these domains. The authors reviewed 37 studies examining the relationship between acquiring multiple chronic conditions and functional decline, as well as the extent and predictability of experiencing multiple health issues about future functional decline, which showed a consistent significant positive correlation in both scenarios.

1.3.2 Societal impact of multimorbidity

The societal impact is related to the recordings of increased healthcare utilisation (Wang et al. 2014), hospital admissions (Violan et al. 2014; Willadsen et al. 2016) and longer hospital stays (Smith et al. 2010) as well as with the unintentional harm by implemented medical treatment or interventions like polypharmacy, referred to as iatrogenesis (Abad-Díez et al. 2014). For example, current estimates have shown that consultations involving patients with multimorbidity tend to be more frequent than all other patients cohorts (Soley-Bori et al., 2020;), account for approximately 32% of annual consultations in primary care (Bower et al. 2011), followed by increased prescription rates associated with the management of multiple chronic conditions. Indicatively, having multimorbidity has been shown to double the expected healthcare usage (OR=2.56) in comparison to patients having 0-1 morbidities (Soley-Bori et al., 2020). Another study has shown that healthcare usage from people with multimorbidity equates to 70% of national healthcare costs (Engamba et al. 2019). Given the societal impact of an NHS experiencing excessive demand and insufficient funding, and with predictions that this will only worsen (Charlesworth et al. 2018), more effective prevention and management of

multimorbidity would have considerable societal benefit through mitigating NHS demand.

1.4 Epidemiology of Multimorbidity

The most common narrative accompanying the introduction of someone with multimorbidity follows a description of it as a prize/price situation. This narrative suggests that multimorbidity is an unintended outcome of the advancement in biomedicine (Ahmadi et al. 2016) of previous century (Fortin et al. 2012). Firstly, it regards the eradication of infectious disease as the primary concern of curative medicine (Marengoni et al. 2011, Wang et al. 2015; Afshar et al. 2015). Secondly, it highlights the life-prolonging advancements in modern medical care (Grant et al. 2011), which have resulted in increased life expectancy (Whitty et al. 2020). This implies that, as the largest subset of chronic conditions (Barnett et al. 2012), multimorbidity is the inevitable price of living life longer (the 'prize').

Epidemiological studies on multimorbidity prevalence provided further support to this narrative, with approximate 54% of the elderly population in England exhibits multi-morbidity showing a positive association between age and multimorbidity (Soley-Bori et al., 2020). In numerous studies (Barnett et al. 2012; Wang et al. 2015) and prominent systematic reviews (Fortin et al. 2012; Salisbury et al. 2011), age consistently emerged as the sole constant contributor to the rise in multimorbidity prevalence rates.

However, a secondary outcome observed in many epidemiological studies of multimorbidity prevalence rates in the wider population (Barnett et al. 2012; Agborsangaya et al. 2012), subtly challenges the narrative that older age drives multimorbidity prevalence, and highlights that multimorbidity is not only a geriatric health issue (Mick, 2019; Blarikom et al. 2023). These studies showed that while the prevalence of multimorbidity increases with age, the majority of people suffering from multiple conditions are of working age (<65 years) (Agborsangaya et al. 2012; Barnett et al. 2012; Willadsen et al. 2016). For example, Adams et al. (2017) found that the 60% of their adult participants age under 65 years old identified as suffering from multimorbidity, which is equivalent to 80% of the under-65 adult population. Similarly, Agborsangaya et al. (2012) demonstrated an increased multimorbidity rate of 70% within the specific cohort of under 65 years old. In turn, Barnett et al. (2012) revealed that

although the frequency of multimorbidity was higher at older ages, in absolute numbers, more under-65s experienced multimorbidity than their older counterparts.

These findings underscore the significance of multimorbidity as not just a matter confined to the elderly but as a critical public health concern (Whitty et al., 2020). This is especially salient given compelling evidence that people with multimorbidity constitute the largest segment of those affected by chronic conditions (Barnett et al. 2012), estimated to approximate the 55% of them (Buffel du Vaure et al. 2016). Such estimations gave impetus to the most common expression that accompanies multimorbidity within the epidemiological contexts, portraying it as the "norm rather than the exception" among patients with chronic conditions. (Barnett et al. 2012; Violan et al. 2014; Buffel du Vaure et al. 2016).

As such the critical implication of the above discussion lies not in whether someone will acquire multimorbidity in older age (as none are exempt) (Ages, 1999). Rather, we need to understand the extent of the differential impact of multimorbidity by age, sex, socio-behavioural factors, and the new challenges this may bring to current healthcare systems. For this to be possible, it is important to accurately measure multimorbidity (Weis et al. 2014).

Despite numerous efforts, researchers are yet to reach consensus on a standardised measurement process and the operational definition for multimorbidity (Diederichs et al. 2011; Sinnige et al., 2013; Abad-Díez et al. 2014). This absence of standardisation presents a notable methodological hurdle, with some researchers acknowledging the inevitability of subjectivity in multimorbidity measurement (Fortin et al., 2014; Pati et al., 2014). Indicatively, two systematic reviews have argued that operational definitions should be grounded on the outcome of interest and data availability (Diederich et al. 2011; Huntley et al., 2012).

1.5 Operational definition

There are four main issues related with the operational definition that researchers tend to debate. The first critical aspect concerns the number of morbidities to be included within multimorbidity indices. The range is enormous. Some studies incorporate as few as four (Agborsangaya et al. 2012) and others as many as 335 (Violan et al., 2014) or all

that are available (Fortin et al. 2012). A study examining 39 existing multimorbidity indices found that the mean number of morbidities used was 18.5 (Buffel du Vaure et al., 2016). In over half of the studies, only eight physical conditions, such as diabetes mellitus, stroke, cancer, chronic obstructive pulmonary disease, hypertension, coronary heart disease, chronic kidney disease, and heart failure, were encompassed, while approximately 21.5% of the studies overlooked any mental health condition (Skou et al. 2022). This variability inevitably impacts prevalence rate estimations, creating incomparable figures ranging from 23% to 98%, that vary with setting and populations under investigation (Diederich et al. 2011).

This has signified the importance of determining the minimum number of chronic conditions included in multimorbidity indices to allow accurate results. This inquiry has been explored in two systematic reviews (Diederich et al., 2011; Fortin et al., 2012). The former suggests the inclusion of at least the 11 most prevalent chronic conditions: cancer, diabetes mellitus, depression, hypertension, myocardial infarction, chronic ischemic heart disease, heart arrhythmias, heart insufficiency, stroke, COPD, and arthritis. Fortin et al (2012) propose the inclusion of the 12 most prevalent conditions based on researchers' data, without further specification.

A cross-sectional study by Harrison et al. (2014) comparing these suggestions found that it was not particularly influential when applied to the definition of multimorbidity as two or more conditions (MM2+). However, when the using the definition of three or more conditions (MM3+), both suggestions did not accurately estimate the prevalence. Therefore, Harrison et al. (2014) recommended using all available morbidities if applying the MM3+ definition. The implication, which was echoed by several researchers such as Fortin et al. (2012), Shadmi (2013), and Skou et al. (2022), is clear: the MM2+ definition lacks significant discriminatory power. Consequently, a distinct operational definition should be proposed to offer better clinical distinction between patients with multimorbidity.

Related to this discussion, the second major debate concerns the cut-off point set to distinguish people with multimorbidity from those without. While the most common cut-off point is the presence of two or more morbidities in a single individual (MM2+) (Sinnige et al. 2013), alternative cut-off points such as three or more (MM3+) or even

four or more (MM4+) have been proposed to better differentiate cases (Fortin et al. 2012).

Fortin et al. 2012 addressed this methodological issue in their influential systematic review. They demonstrated that when the typical definition MM2+ was applied a depiction of an S-curve emerged when examining the prevalence of multimorbidity examined in relation to age. Specifically, prior to the age of 40, multimorbidity prevalence remained relatively low, estimated at around 20% of the population. However, from this point onward, there was a sharp increase in prevalence, reaching a plateau around the age of 70, where approximately 75% of the older population are affected by multimorbidity. Interestingly, when MM3+ was applied this S plateau did not appear. To reconcile this discrepancy, researchers, suggest the simultaneous usage of both terms.

An alternative term, Complex multimorbidity, is used to denote the co-occurrence of three or more conditions affecting at least three different organ system as assessed by the Cumulative Illness Rating Scale (CIRS) (Storeng et al. 2020). However, the most comprehensive systematic review today (Ho et al. 2021), that comprised 566 studies on multimorbidity showed that the term of Complex multimorbidity is far less frequently used than simple count measurements. In response, Chapter 4 presents evidence on the prevalence of multimorbidity based on traditional count (MM2+ and MM3+) and Complex multimorbidity definitions.

Linked to this, the third issue regards the development of numerous of multimorbidity indices that prioritise the severity of disease as a key component of variation between people with multimorbidity. Aside from the already presented Cumulative Illness Rating Scale for assessing the Complex multimorbidity, examples include the Charlson Comorbidity Index, the, the Chronic Disease Score, RxRisk Model, and the Duke Severity of Illness Checklist (Fortin et al. 2012; Sinnige et al. 2013). However, the weighting in these indices varies, with some based-on factors like mortality, others on hospital stays, quality of life or even body-system domains that morbidities affect (Diederichs et al. 2011).

Examining which of the above mentioned multimorbidity indices are suitable for research within primary care setting, Huntley et al. (2012) showed that different methods are best suited to different outcome of interest. Indicatively, the Adjusted

Clinical Groups (ACG) and Charlson index was more suitable for examining care utilisation, ACG was better for investigating mortality and Charlson index better for quality of life. Interestingly Huntley et al. (2012) found that disease count measurements performed as well as Complex multimorbidity indices in accurately predicting most outcomes. Their main suggestion to increase validity was the combined usage of various measures (as performed in Chapter 4).

The last issue concerning the variability in the operational definition of multimorbidity, and its accompanied indices regards with whether a mixture of morbidities, symptoms and risk factors are included within a specific multimorbidity index. Willadsen et al. (2016) have shown that, although most multimorbidity's operational definitions are based on morbidities, it is common for symptoms and risk factors to also be included, with risk factors typically outnumbering symptoms. This observation was further supported by Sinnige et al. (2013) who found that in 62% of the articles they examined, there was high variability in the types of symptoms included in multimorbidity measurement tools. The rationale for these additions is that morbidities alone cannot adequately reflect patients' experiences and needs, thus symptoms are deemed necessary additions. The inclusion of risk factors, a characteristic or exposure that increases their likelihood of suffering from a disease (Olivares et al. 2017), addresses the preventative aspect of multimorbidity measurement. However, caution is required to ensure that the measurement tool does not become overly focused on prevention at the expense of accurately reflecting the current disease burden (Willadsen et al. (2016).

A quotation from Willadsen et al. (2016) offers an appropriate summary of the current situation for operational definitions of multimorbidity:

> *'Existing multimorbidity definitions may seem more suitable for epidemiological research than for clinical work. In the light of the increasing prevalence and burden of MM, definitions which are more useful in daily practical work could be more helpful for both clinicians and patients' (p.113).*

1.6 Prevalence of multimorbidity – socio-economic and sex effects

As section 1.5 makes clear, prevalence rates for multimorbidity depend on the operational definition and measurement tool used (Salive, 2013; Fortin et al 2014). However, certain findings are consistent despite this variability. Besides age, other

factors consistently identified as strong determinants of multimorbidity include low socioeconomic status (Coventry et al. 2014) and female sex (Reis-Santos et al., 2013; Violan et al., 2014). For example, Pearson-Stuttard et al. (2019) found that individuals in lower socioeconomic strata have a 47% higher likelihood of developing multimorbidity. Additionally, Barnett et al. (2012) demonstrated that this occurrence may manifest even 10-15 years earlier in individuals residing in more deprived areas compared to those in higher social strata, confirming suggestions by Salisbury et al. (2011) and later reaffirmed by Whitty et al. (2020). Chan et al. (2019) supported this evidence, indicating a lower threshold for developing multimorbidity among socially disadvantaged individuals, with women experiencing this onset two years earlier and men one year earlier. Singer et al. (2019) also explored the socioeconomic impact, examining household wealth as a proxy parameter in individuals above 50 years old in England.

Among the socioeconomic indicators, none appeared as robust as education level. Pathirana and Jackson (2018) demonstrated in their systematic review that differences in educational attainment (low versus high) were associated with a 64% increase in the likelihood of multimorbidity among those with lower education levels. This consistency is particularly noteworthy given that other socioeconomic parameters did not consistently yield the same outcomes. For example, Wang et al. (2014) found contrasting results when examining household income in the Chinese population, where individuals with higher incomes unexpectedly exhibited increased probabilities of developing multimorbidity. Similarly, Violan et al. (2014), in their examination of the socioeconomic impact on multimorbidity stratified by sex, failed to identify a socioeconomic trend associated with men's multimorbidity.

These discrepancies have led some researchers to posit alternative explanations that could intervene and influence the association between socioeconomic status and multimorbidity. For instance, Barnett et al. (2012), while noting a positive association between areas of deprivation and the risk of multimorbidity, questioned whether this reflects behavioural factors such as smoking, which are more prevalent in more deprived population groups. Similarly, Fleitas et al. (2022), in their scoping review, found that behavioural theories were the most common explanation for observed socioeconomic inequalities in multimorbidity. Katikireddi et al. (2017) took this further by estimating that health risk behaviours such as smoking, nutrition, alcohol consumption, physical

activity health risk behaviours (SNAP-HRBs) and body mass index (BMI) collectively accounted for a 40.8% mitigation of the association between low socioeconomic status and multimorbidity.

Differences in multimorbidity prevalence by gender or sex are consistently observed, with a greater prevalence in females compared than in men (Marengoni et al., 2011; Barnett et al., 2012; Wang et al., 2014; Mick, 2019). Differences in multimorbidity rates have ranged from 19.2% for females to 15.6% for males in one study (Agborsangaya et al., 2012), and from 53.3% for females to 41.7% for males in another (Violan et al., 2014).

In summary, it is consistent across various studies, that being older, female, and from lower social strata you have a higher likelihood of experiencing multimorbidity (Marengoni et al., 2011).

1.7 Settings of investigation and multimorbidity prevalence

Multimorbidity has been examined in various settings. Studies have targeted the general population usually via health surveys or they investigated registered primary care populations, institutionalised populations in hospitals and nursing homes, and used data from health surveys and electronic health records. The high variability in study outcomes make some researchers like Fortin et al. (2014) to admit that due to numerous methodological issues related with multimorbidity measurement, the observed discrepancies are more likely to be methodological artifact (not a reflection of the reality).

Specifically, Agborsangaya et al. (2012), Fortin et al. (2014) and Mokraoui et al. (2016) consistently observed differences in multimorbidity prevalence rates between primary care settings and general population studies. Even after employing various operational definitions, Mokraoui et al. (2016) found that a significant 10% gap in prevalence rates between settings persisted. Meanwhile, Schram et al. (2008), investigated the impact of settings and registry characteristics on multimorbidity among older adults. They found comparable rates between studies conducted in the general population (ranging from 56% to 72%) and those in general practices (ranging from 56% to 66%). However, they noted substantial disparities in prevalence rates, with nursing homes exhibiting the highest prevalence and hospital settings showing notably lower rates (22%).

Interestingly, in a study conducted by Violan et al. (2013) exploring the differences between data sources in health surveys and electronic health records. It found that the primary inconsistency in prevalence results was linked to age. Notably, a significant difference was observed in the younger population, where prevalence rates differed by 17%. Health surveys exhibited a prevalence rate of 60%, higher than that of electronic health records with 43%. However, this discrepancy reduced to 8% in older populations (91% versus 83%) still favouring health surveys.

Finally, despite the recommendations of two systematic reviews (Fortin et al. 2014 and Violan et al. 2013) advocating for electronic health records and primary care data as the most accurate representation of multimorbidity prevalence, especially at the local population level caution is warranted. These reviews highlighted potential factors that may influence data reliability, including issues related to the completeness and coding of the records. For example, studies have been challenged on issues of double counting in electronic health records that might limit understanding of multimorbidity (Calderón-Larrañaga et al., 2018). This can produce prevalence estimates and skewed multimorbidity scores, which can misinform clinical decision-making and healthcare resource allocation (Payne et al., 2020). Use of systems for standardised data coding, such as EMIS, and their utilisation by experts who can perform advanced analytics to detect and correct duplicate entries before the research manipulation of data can mitigate doubling counting, securing more reliable investigation of multimorbidity (Jin et al., 2022; Hanlon et al., 2022) (see Chapter 4 for further insights).

1.8 Mechanisms/pathophysiology and clustering of morbidities

The heterogeneity of the treatment outcome between people with multimorbidity (Weis. et al. 2014), even if they have received the same diagnosis (Levenstein et al. 1986), is well-acknowledged in multimorbidity inquiry. Understanding the mechanisms and pathophysiology of multimorbidity is challenging due to the diverse nature of patients.

A typology initially proposed by Van den Akker et al. (1996) provides a functional classification system regarding the relationship between morbidities (Van den Akker et al. 1996; Schäfer et al. 2010; Jakovljević & Ostojić, 2013). In summary, multimorbidity/comorbidity can be expressed in various ways:

- Concurrently, indicating the random coexistence of morbidities.

- Aetiologically, prioritising the investigation of the impact of a pathological agent on multimorbidity.
- Through clustering, signifying statistically significant relationships among morbidities without causality.
- Causally, suggesting distinct morbidities clustering that share a common pathophysiological pathway.
- In a complicated course, where the existence of a subsequent morbidity cannot be justified without the presence of its precursor.

To overcome the clinical and methodological constraints arising from simplistic counts and weighted indices, researchers have increasingly adopted data-driven methods (Schram et al. 2008; Agborsangaya et al. 2012; Violán et al. 2013; Sinnige et al. 2013). These approaches are based on the premise that certain morbidities exhibit associations beyond random chance. Initial efforts have focused on identifying the most prevalent combinations of dyads, triads, and quartets through the observed-expected ratio technique. This technique assesses the co-occurrence of morbidities in a manner greater than expected. For example, in a given population, if 30% have hypertension and 45% have heart disease, then the expected proportion of individuals with both morbidities in the general population would be 30% x 45% = 11.25%. Therefore, any co-occurrence of hypertension and heart disease exceeding this predicted probability is a clear indication of clustering.

Nevertheless, exhaustively examining all potential combinations, which leads to calculations exponentially increasing in magnitude, particularly with a large sample size, is impractical. For example, with 20 morbidities, the required calculations would amount to 380 for dyads, 1140 for triads, and 4845 for quartets (Cornell et al., 2009).

Therefore, researchers turned to more advanced statistics. Among the most prominent approaches to identify potential underlying patterns in the distribution of multimorbidity are cluster analysis and exploratory factor analysis. Their primary objective is to uncover such multimorbidity patterns with the aim of gaining a deeper understanding of their synergistic effects and, ultimately, to develop tailored interventions (Sukumaran et al. 2024) or to inform the development of future multimorbidity guidelines (this is explored further in Chapter 5).

Although there were differences in the disease clusters observed across various studies, a systematic review on 14 studies revealed three consistent patterns (Prados-Torres et al. 2012). These patterns reflected the clustering of cardiovascular and metabolic syndrome-related diseases, mental health conditions, and musculoskeletal disorders. There are two primary criticisms of this approach. First, there is limited replicability of patterns generated by individual studies, primarily due to variations in methods and datasets used (Skou et al., 2022). Second, the multimorbidity concept is reduced to an amalgamation of prevalent morbidities, raising questions about whether this represents another instance of a reductionist approach to a complex phenomenon (Blarikom et al. 2023).

1.9 Multimorbidity as challenge to current healthcare systems

The inadequate definition and measurement of the multimorbidity phenomenon has rendered it largely overlooked by researchers, policymakers, and healthcare providers. Consequently, the majority of research papers, clinical guidelines, and healthcare practices continue to be guided by reductionist approaches that focus on single diseases.

Increased interest among public health researchers and policymakers regarding this issue (Fleitas et al. 2022) is mainly driven by the adverse effects and substantial costs linked with it (Vogeli et al. 2007; Fortin et al. 2014; Glynn et al. 2011), and the significant clinical and organisational challenge of the current monomorbid healthcare system (Smith et al. 2010). This challenge is directly related to the heightened complexity accompanying the management of multiple chronic conditions and the subsequent increased demands for time and resources required to adequately address the complex needs of patients with multimorbidity (Mann et al. 2016; Doos et al. 2014).

Despite the increasing prevalence of multimorbidity, surveillance (Agborsangaya et al. 2012) and diagnostic code systems (Badalà et al. 2008) predominantly adhere to a single chronic condition approach. This stance aligns with the healthcare system’s disease-centredness that prioritise the production and implementation of evidence based single-disease guidelines (Weis et al. 2014). A condition that undoubtedly prioritises "cure" over "care" for chronic conditions management (García-Goñi et al. 2012). Adherence to single-disease guidelines has created problems (Du Vaure et al.2016), most prominent of which is polypharmacy. Polypharmacy has emerged as a significant concern because

individuals with multimorbidity often face an increased risk of adverse effects through being prescribed a range of medications to address their numerous conditions. Dumbreck et al, (2015) studied potential drug-disease and drug-drug interactions within specific index conditions (e.g., diabetes). The authors revealed that while adverse effects due to drug-disease interactions were rare, just for type 2 diabetes medications, they identified 133 different drug-drug interactions. Yet, few researchers currently argue that polypharmacy may contribute to the perpetuation or even generation of multimorbidity (Blarikom et al., 2022). From a different perspective, Hughes et al. (2013) analysed the recommendations outlined in five NICE guidelines (type-2 diabetes mellitus, secondary prevention for people with myocardial infarction, osteoarthritis, chronic obstructive pulmonary disease, and depression). They found that significant treatment burden arises even when adhering to recommendations from just two guidelines. Importantly, they observed a lack of consideration for potential comorbidity effects or a person-centred care approach. In summary, this discussion highlights the failure of the present healthcare system to adjust and restructure itself towards a more person-centred approach. This shift is essential for effectively managing the complex demands of the ongoing crisis of multimorbidity (Shadmi, 2013).

Furthermore, people with multimorbidity often experience fragmented care delivery (Smith et al. 2010) characterised by a lack of continuity (Salisbury et al. 2011) and coordination between services and healthcare providers (Lindvall et al. 2016). This results in a burdensome number of consultations with various healthcare providers (Vogeli et al. 2007), with potential for conflicting recommendations and treatments, which at times, can even jeopardise patient safety (Abad-Díez et al. 2014). For instance, findings from the Quality and Outcomes Framework (QOF) indicate that individuals with multimorbidity, on average, attend 9.4 primary care consultations annually, compared to 3.8 consultations among those without multimorbidity (Doos et al. 2014). Other estimates have revealed that between 1995 and 2010, the proportion of adults with multimorbidity who take five or more medications has risen from 11.4% to 20.8%, while those taking ten or more medications have increased from 1.7% to 5.8% (Guthrie et al. 2015).

Quality of care measurements fail to address these unintended iatrogenic consequences (Badalà et al. 2008). Implementation of Quality Outcome Framework (QOF) criteria,

primarily aims to enhance the cost-effectiveness of healthcare services in a bureaucratic manner, assigning economic value to patients' biomarkers and thus perpetuating the provision of healthcare providers within a biomedical model of care (Blarikom et al. 2023). During a conference convened by the Society of General Internal Medicine to explore optimal assessment of care quality for patients with multimorbidity, experts acknowledged the challenges of balancing rigorous quality standards with the complexities of managing multimorbidity. One of the key takeaways from the conference, however, was the recognition of the importance of personalised care that considers factors beyond mere medical conditions (Werner et al. 2007).

The implication is clear: to ensure the provision of safe and effective care for people with multimorbidity, healthcare system's need a shift from the current disease-centred approach to a more person-centred model. This shift requires healthcare providers to realign their clinical practice to effectively address the complex needs of patients with multimorbidity, thereby reducing the treatment burden and associated iatrogenic risks (Badalà et al. 2008; Weis et al. 2014).

Multimorbidity has that potential. It is forcing researchers and practitioners to break down disciplinary barriers and to promote interdisciplinary collaboration (Prochaska, 2008), challenging the prevailing single disease paradigm, which predominantly relies on medical inquiry for knowledge generation (Fortin et al. 2012). However, embracing this shift requires a fundamental change in our mindset as researchers and practitioners, as well as courage to embrace diverse concepts and practices across disciplines (Whitty et al. 2020). Such an innovative perspective, laying the groundwork for the emergence of new developments in multimorbidity inquiry, was proposed by Blarikom et al. (2023). They argue against the ongoing, fruitless pursuit of defining multimorbidity solely with biomedical terms, portraying it as an organic entity within patients' physical bodies. Instead, they advocate a turn towards understanding multimorbidity as an experience shaped by the gap that emerges between medical policy and the lived realities of patients with multimorbidity as they attempt to navigate an uncoordinated and fragmented healthcare system.

This approach aligns with the afore-mentioned novel multimorbidity definition, inspired the current research, and echoes the views of scholars such as Loprinzi (2015), who advocates for a unified framework that integrates multimorbidity and multibehaviours

inquiries. This proposal serves as a driving force for the necessary shift towards person-centred care for people with multimorbidity, emphasising the need for systemic modifications. Essentially, this joint multimorbidity-multibehaviours inquiry, offers an alternative to current medicalised provision of care for people with multimorbidity; a paradigm shift to a more salutogenic perspective that integrates behavioural theories into care. This redirects attention to factors that promote human health and well-being, rather than solely emphasising those that contribute to disease or illness. For example, Dale & Lee (2016) have proposed an integrated care model that embeds behavioural healthcare within primary healthcare, while as member of a multidisciplinary team can support the psychological and behavioural parameters attached to multimorbidity, such as the acquisition of healthier lifestyles and the intense support of patients to improve their self-management processes.

1.10 SNAP-HRBs: key behavioural determinants of multimorbidity

Health risk behaviours (HRBs) such as smoking, poor nutrition, alcohol misuse, and physical inactivity (SNAP) have long been recognised by the scientific community, health policymakers and practitioners as significant contributors to chronic disease morbidity and premature mortality (Morris et al., 2016; Pronk et al., 2004; Froshaug et al., 2009; Jepson et al., 2010).

In England and Wales, approximately one-third of premature deaths under the age of 75 are estimated to be associated with SNAP-HRBs. Owen et al. (2012) estimated the annual cost to the NHS attributable to each of these SNAP-HRBs: £2.7 billion for smoking, £4.2 billion for obesity, £1.06 billion for physical inactivity, and £1.7 billion for alcohol misuse. Randell et al. (2015) demonstrated that around 70% of primary care patients are engaged in SNAP-HRBs, resulting in significant attributable costs. These estimations are concerning, especially considering the small minority of the population that do not engage in any of the four SNAP-HRBs; estimated to be 3% of the population in one study (Prochaska, 2008). This aligns with the suggestion by Randell et al. (2015) that almost adults (95.5%) consulting for routine primary care are eligible for interventions related to risky health behaviours.

However, few of these individuals are assessed or receive interventions for health behaviour change within primary care. Several studies support this notion, and reveal

marked variability in the frequency of primary care assessment for each of the SNAP-HRBs. For example, while Denney-Wilson et al. (2010) found that less than 20% of patients are routinely asked about drinking habits, assessment of alcohol consumption was reported in 76% of cases by Bartlem et al. (2015). Fruit and vegetable intake was consistently least assessed, in only 26% of cases. Regarding smoking, around 66% of patients were routinely asked about their smoking status (Denney-Wilson et al., 2010). However, even among smokers at risk for COPD, 50-72% receive no behavioural change intervention, despite the high acceptability of preventive care among clients (86-97%) (Bartlem et al., 2015). Primary care settings appear an ideal environment for implementing health-promoting interventions aimed at modifying health risk behaviours, as over 90% of older adults visit their healthcare providers at least once a year (Morey et al., 2006).

Several factors may contribute to the lack of behaviour change support in primary care. Many healthcare providers express a lack of belief in patients' ability to change unhealthy behaviours as an excuse for not providing behaviour change intervention. Often, a lack of time is identified as the barrier to dealing with the complex needs of people with multimorbidity, or insufficient training to effectively counsel patients (Morey et al., 2006; Spring et al., 2012).

Alternatively, the literature suggests the presence of the "wake-up call" hypotheses as potential explanations for the limited implementation of behavioural change interventions in primary care. These hypotheses propose that a diagnosis could prompt individuals to discontinue risky behaviours and adopt critical lifestyle changes, as part of secondary prevention treatment. However, studies conducted by Newsom et al. (2012) revealed that most individuals do not make substantial lifestyle changes following a diagnosis of a serious chronic disease, with only 40% of smokers successfully quitting. Similar findings were reported by Dontje et al. (2016) regarding women and their engagement in physical activity after being diagnosed with a chronic condition. Simply put, these findings underscore the need for intensive efforts from healthcare providers to initiate and sustain lifestyle improvements among patients (Newsom et al., 2012), particularly those with multimorbidity who may have been engaging in SNAP-HRBs before their diagnosis or who need to implement SNAP health behavioural changes as part of their therapeutic regimen following diagnosis.

1.11 Multibehaviours

Investigations into the individual SNAP-HRBs in the context of multimorbidity risk have revealed mixed findings. Hudon et al. (2008) did not find a significant association between physical activity and multimorbidity risk, which contrasts with other studies that report an inverse relationship between physical activity and the risk of multimorbidity (Cimarras-Otal et al., 2014; Loprinzi, 2015; Dhalwani et al., 2016). Similar inconsistencies have been observed for other individual SNAP-HRBs. While Garcia de Siqueira et al. (2016) reported an association between multiple chronic conditions and current or previous tobacco use, Study et al. (2016) found a strong association between smoking and multimorbidity among former smokers only. Additionally, Fortin et al. (2014) found no association between alcohol consumption and the presence of multimorbidity for men nor women, a finding corroborated by Katikireddi et al. (2017).

Similar to morbidities, strong evidence suggests that SNAP-HRBs possess multiple, rather than singular properties. Behavioural scientists have long suspected that most individuals engage in more than one SNAP-HRB, implying that combining multiple unhealthy behaviours may have synergistic health effects, thereby increasing the risk of chronic disease (Griffin et al. 2014). Morris et al. (2016) estimated that half of participants in their sample (51%) exhibited one or more lifestyle risk behaviour, with 10% having two or more concurrent risk behaviours. Cluster analyses on SNAP-HRBs have further confirmed that these modifiable lifestyle-related health risk factors tend to cluster, increasing the likelihood that SNAP-HRBs co-exist simultaneously (Pronk et al., 2004). In a systematic review of 32 cross-sectional and longitudinal UK studies investigating the cluster properties of SNAP-HRBs, Meader et al. (2016) showed that the most common combinations of risk behaviours investigated were: alcohol and smoking, physical activity and smoking, and diet and smoking.

The implications of the synergistic effects of SNAP-HRBs on multimorbidity are significant, primarily because they play a dual role as modulators - either synergistically contributing to its development or synergistically mitigating its impact (Pronk et al. 2004). On one hand, an increasing number of studies in recent years have shown that the accumulative presence of SNAP-HRBs is producing a strong dose response association between the number of SNAP-HRBs and multimorbidity risk (Agrawal et al. 2016; Katikireddi et al. 2017; Adams et al. 2017). On the other hand, ideas mainly derived

from behavioural science suggested that multiple health behaviour change interventions may produce the reverse synergetic effect as such mitigating the impact of multimorbidity sharing common underlying protective pathways (Lee et al 2009). Furthermore, there is strong evidence that multiple health behaviour change interventions are more effective for secondary prevention (Prochaska et al. 2008; Kipping et al. 2015), while the adopting healthier lifestyles can improve well-being (Froshaug et al. 2009), another important parameter regarding the proposed salutogenic solutions to multimorbidity treatment (Sauvage & Ahluwalia, 2016).

In summary, multimorbidity burdens current healthcare systems are not designed to deal with this complexity. Developing healthcare systems to improve prevention and treatment of multimorbidity requires a pragmatic approach to operational definitions and measurement. Rather than adhering rigidly to theoretical or disciplinary silos, it is important to prioritise addressing the practical needs in daily clinical practice. Enhanced validity of outcomes can be achieved through examination of multimorbidity operational definitions (Fortin et al. 2012) as well as the combining available measurements to a given inquiry (Huntley et al. 2012). Furthermore, seeking all possible aetiological, causal, and experiential linkages between morbidities and if necessary, their potential pathogens or risk factors, such as multibehaviours in the present case, is a clinically valuable inquiry.

1.12 Integrated care as response to multimorbidity

The provision of Integrated healthcare was the key response that many high-income countries, including the UK, adopted to address the chronic disease epidemic, aligning themselves with WHO's recommendations (Tsiachristas et al. 2018).

However, it is widely accepted today that these integrated care models that most focus on single long-term morbidities following mostly the Vagner's chronic care model, are insufficient for addressing the complex needs of people with multimorbidity, potentially threatening the provision of optimal care for the specific cohort.

It is acknowledged that any effort to provide integrated care for people with multimorbidity must first successfully address healthcare system fragmentation, while simultaneously promoting coherent continuity of care by integrating services across

medical specialties and disease areas and beyond, to meet the needs of social care Dambha-Miller et al. 2021).

This means the structural shift of the entire health system from a disease-centred provision of healthcare to a person-centred one. This approach primarily requests healthcare delivery that is respectful and responsive to the preferences, needs, and values of people with multimorbidity, ensuring these factors will guide all clinical decisions (van der Heide et al. 2018). In short, this is a multifaceted task needed to address various emerging challenges at functional, organisational, or clinical levels, requiring integrations ranging from simple collaboration between services, to full-scale systemic integration (Struckmann et al. 2018).

In a taxonomy provided by Rijken et al. (2018) to profile the integrated care approach that targets people with multimorbidity found, there are three main types of integrated approaches: a) those targeting any combination of chronic conditions; b) those targeting indexing chronic condition and all possible comorbidities; c) those targeting specific chronic conditions. By examining the differences and similarities between them, they concluded that targeting integrated care on any form of multimorbidity is most suitable for people with multimorbidity. The main reason was that this generalised approach aligned better with person-centred care due to its emphasis on the provision of comprehensive care and patient involvement in decision making and treatment plans, and lesser to extent, evidence-based practice outcomes (the focus for disease specific practices).

Various integrated care models have adopted different methodologies to enhance person-centred care and involve people with multimorbidity in decision-making. Techniques such as motivational interviewing and narrative counselling have been used to support this shift (van der Heide et al. 2018). However, this also implies that the absence of these skills may pose a barrier to transitioning healthcare from a disease-oriented to a person-centred approach, and some uncertainty of whether care providers are willing to adapt their care delivery practices accordingly.

Based on such sporadic evidence and their expertise, various consortia aimed to develop an integrated model for people with multimorbidity adapting specific elements that constitute the prominent models of single long-term care, such as Vagner's chronic care model. Integrated models specifically for people with multimorbidity such as JA-

CHRODIS Multimorbidity Care Model and the SELFIE framework emerged. The former is more targeted on the development and/or improvement of practices at the clinical level, while the latter less operationally focused, focuses on how to address contextual conditions (Tsiachristas et al. 2018).

For example, the consortium of Integrated Multimorbidity Care Model developed by the European Joint Actions CHRODIS concluded five principal components as the most important elements to be adopted regarding support for people with multimorbidity were: a) shared health records among providers; b) self-management support; c) care coordination (including the exploitation of social and community resources); d) shared decision; e) comprehensive assessments and provision of is a key example (Rijken et al. 2021; Palmer et al. 2018).

In addition, the International Foundation for Integrated Care has suggested that to achieve the best health outcome for people with multimorbidity, an integration of both the provision of comprehensive, continuous and coordinated care alongside more public health-oriented support for lower other non-clinical based risks (e.g., those derived from the acquisition of unhealthy lifestyles) must be jointly applied under the umbrella term of integrated care. This emphasises the significance of both temporality (continuity of care) and spatial (place-based care) dimensions as key ingredients of a successful integrated model for people with multimorbidity (Lennox-Chhugani, 2021).

In the UK, integrated care systems were established in 2022 with many of the above characteristics. The Integrated Care System (ICS) model is a whole system solution following the non-specific disease approach and incorporating both health and social care or temporal and spatial healthcare dimensions. However, in parallel, polices like the Major conditions strategy was also applied focusing on the specific group of six conditions such as cancers, cardiovascular disease (CVD) (including stroke and diabetes) musculoskeletal disorders (MSK), mental ill health, dementia, and chronic respiratory disease (CRD) that account for the 60% of ill health and early death in England (DHSC, 2023).

NHS Health Check programme is such an initiative targeting adults in England for cardiovascular disease prevention and health risk assessment. It has been criticised for being focused on individual-level intervention without adequately addressing broader social factors, thus risking widening of health inequalities (Perry et al., 2014). Experts in

the field like Katikireddi reinforce this by arguing that public health efforts must not solely focus on behavioural modifications but also to target on how to tackle social inequalities that shaping those behaviours and health outcomes as well (Katikireddi et al., 2013).

Evidence for existing integrated care models highlights that although they may increase patient satisfaction, accessing and perceived quality of care among people with multimorbidity. However, barriers regarding inter-professional collaboration and patient care continuity remain (Baxter et al., 2018), their effectiveness on clinical outcomes is still questioned (Tsiachristas et al., 2018), and proper integration seems more a theoretically based intention rather a practical reality (Stokes et al., 2016).

Integrated care systems aim to address all these by establishing 42 local integrated care partnerships around the country, joining the statutory healthcare sector, local council, social care providers, and voluntary sector under a common goal of improving the health and well-being of the local population. Within this framework, Integrated Care Boards (ICBs) consist of representatives from NHS organisations responsible for designing and implementing a five-year healthcare plan tailored to local needs. Their role is to align mainstream healthcare services with the broader strategy of the local Integrated Care Partnership, ensuring a coordinated and community-focused approach to care (National Health Service, n.d.).

As Dambha-Miller et al. (2021) stressed, key components for the successful of any whole system strategy of the integrated care systems approach are: a) the empowerment of frontline staff to lead a bottom-up change by having the flexibility to fill the connection gaps between services when feel they must; b) fine coordination of same level services (e.g., GP practices, hospitals, community pharmacies) across entire system that includes statutory services, community, and individual patients

Social prescribing has emerged to fulfil this role, linking statutory services with local communities and promoting both the spatial dimension of coordinated care and the temporal one of continuity. In short by placing social prescribing into the national healthcare system, it signals a redirection towards a more comprehensive response to the needs of some of the most complex of its users (e.g., people with multimorbidity), promoting services that meet their complex needs, promoting more person-centred coordinated and continuous care (Lennox-Chhugani, 2021).

For achieving this goal social prescribers' key responsibility is to be knowledgeable of the local community services, and to timely signpost people with multimorbidity to accessing services in their community, able to facilitate their self-management needs, (e.g. linking them to services able to support the better management of their health risk behaviours towards the adoption of healthier lifestyles) in order to meet the requirements for secondary prevention (Kiely et al. 2021).

However, as a systematic review has shown, despite social prescribing being a widely accepted service within the UK healthcare system, there is still no robust evidence for its effectiveness, especially for people with multimorbidity (Bickerdike et al. 2017). The authors stressed, "even 'good enough' is severely lacking from the social prescribing literature" (p.15).

In summary, one can argue that integrated care for people with multimorbidity is in a transitioning phase, and a more effective approach is required to address its complexities.

1.13 Aims and objectives

The overarching aim of this thesis was to comprehensively explore the interrelationships between multibehaviours and multimorbidity by investigating their aetiological and causal interrelationships, as well as their combined impact on the healing relationship between healthcare providers and individuals with multimorbidity.

To achieve this, a series of objectives were addressed:

1. To quantify the association between multimorbidity and multibehaviours from the published literature.
2. To examine the combined and cumulative association between multibehaviours and multimorbidity using three different operational definitions for multimorbidity.
3. To examine the patterns of associative multimorbidity-multibehaviours for both sexes.
4. To examine the combined impact of multimorbidity and multibehaviours on the healthcare relationship.

1.14 Thesis structure

To address the above aims and objectives, the present thesis is structured as follows.

Chapter 1 (Literature Review). This chapter presented a review of the literature on multimorbidity and its methodological issues that accompany its definition, setting the scene for the multimorbidity-multibehaviours inquiry, making the case of the thesis aims.

Chapter 2 (Methodology) provides comprehensive account of the methodological underpinning for this thesis, which combines a series of different methods as part of a pragmatic inquiry of multimorbidity and multibehaviours.

Chapter 3 (Study 1) presents a systematic review and meta-analysis that investigated the association between multimorbidity and multibehaviours from the published literature. It highlighted important relationships and methodological considerations, not least the range of approaches to defining and measuring multimorbidity and multibehaviours that have been applied.

Chapter 4 (Study 2) presents analysis of primary care data to investigate the aetiological association of multibehaviours as a pathogen to multimorbidity risk via an epidemiological study.

Chapter 5 (Study 3) further examines primary care data using exploratory factor analysis to investigate the causal relationship between multimorbidity and multibehaviours as revealed by multimorbidity patterns and their shared underlying pathophysiological mechanisms.

Chapter 6 (Study 4) is the final empirical chapter. Situational Analysis is implemented to explore the combined impact of multimorbidity and multibehaviours within the healing relationship between healthcare providers and people with multimorbidity.

Chapter 7 draws on findings from Chapters 3-6 to discuss the findings and contribution of the present thesis, the implications for research and practice, and the overall strengths and limitations of this work.

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Having reviewed the literature that highlights the gaps this thesis aims to address, the following chapter provides a detailed account of the methodology selected.

2. PhD Methodology Chapter Outline

2.1 Introduction

Research is a fundamental aspect of scholarly inquiry that when applied methodologically and in a systematic way, contributes significantly to contemporary understanding, of a specific topic of interest (Kothari, 2004). To do so, an integral aspect of good research regards its research methodology, which has been described as the general steps undertaken by researcher when initiating a research project (Apuke, 2017). The main contribution of research methodology is to serve a comprehensive research approach that outlines the manner in which the research is going to be conducted (Melnikovas, 2018). By incorporating a system of beliefs and philosophical assumptions, the methodological framework forms the conception of research questions and the groundwork for the selection of research methods (Dissanayake, 2023).

Guidance on this task was derived from the methodological framework of research onion model. Research onion model is among those methodological efforts, like the Four Ps of Research (Remenyi et al., 1998); the Three-Dimensional Model (Teddlie and Tashakkori, 2009); and the Research Design Types (Creswell, 2014) that tried to manage the complexity surrounding the variety of existing methods and their underlying philosophies. Their main purpose is to offer comprehensive tools able to elegantly support the revealing of the logic behind researchers' chosen methods and techniques (Melnikovas, 2018; Dissanayake, 2023). And by doing this to secure the development of coherent and justifiable research design.

2.2 The Research Onion Model

Proposed by Saunders et al. (2007), the research onion model (Figure 1) presents graphically in the form of onion, the structural development of all necessary methodological steps. Following metaphorically, a top down process similar to the one of peeling an onion, meaning from the outer layers to the inner layers, a series of choices are provoked that facilitate a thorough research design and methodology (Dissanayake, 2023).

The research onion is comprised by six interconnected and interdependent layers that exist within three broader levels of decision-making that intentionally or unintentionally are made by any researcher (Tengil, 2020; Dissanayake, 2023).

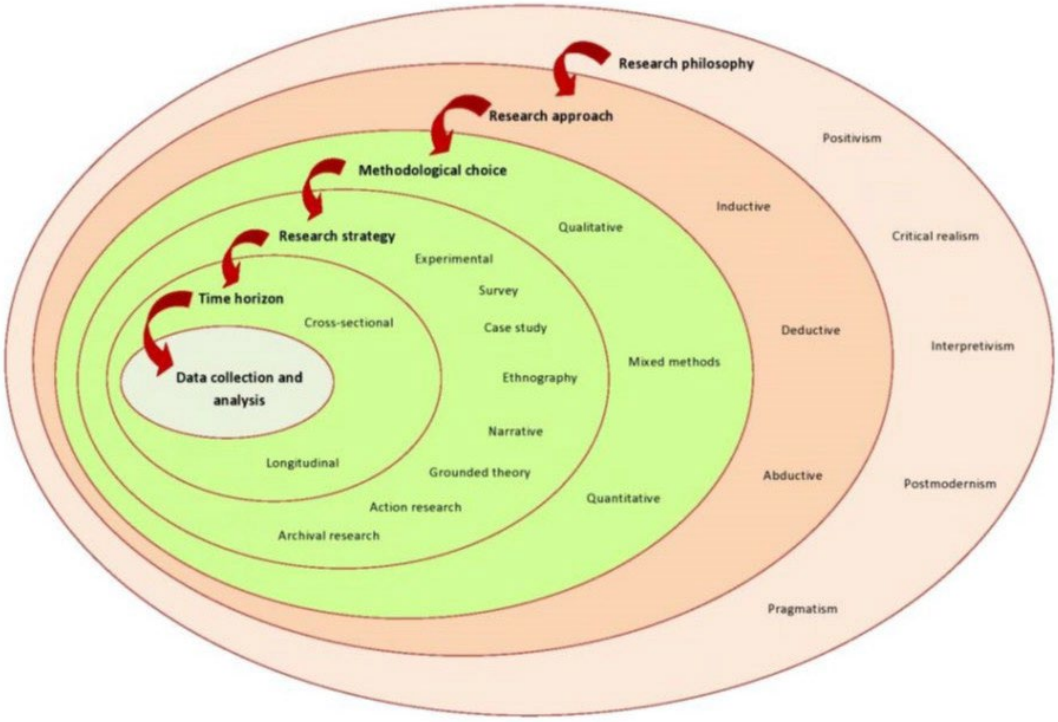

Figure 1. The Research Onion of Mark Saunders

Source: ©2019 Mark Saunders, Philip Lewis and Adrian Thornhill (Saunders et al., 2019)

2.2.1 Outer layers of the Research Onion model

The first two outer layers involve decisions related to the "Research philosophy" or a 'system of beliefs and assumptions about the development of knowledge' (Saunders et al. 2019 p. 130) - supported by scholars who align themselves within a particular philosophy, and concerns the nature of reality (ontological), the knowledge generation (epistemological) and the ethical considerations (axiological) surrounding the research project. And The "approach to theory development" or the manner in which eligible knowledge emerges - in short, whether knowledge is generated via deductive (hypothesis-based), inductive (theory-building) or abductive (empirically tested researcher's theoretical based intuitions) approaches.

These layers are now considered in more detail, with links to the present thesis.

2.2.1.1 Research philosophy

Research onion discusses five research philosophies, including the traditional approaches of positivism and interpretivism and three "newer" philosophies such as critical realism, pragmatism, and post-modernism (Melnikovas, 2018; Tengil, 2020).

Positivism is a philosophical framework, assimilated by natural sciences, and based on the assumption of an observable reality that exists independently, and unaltered by human cognition (Robson, 2009). To reach this reality, research should be scientifically rooted. In other words, this means that reaching reality can be only achieved through a rigorous empirical observation of collected measurable data (Popper, 2005). Methodologically this is translated to a structurally replicable, value-free study design that will permit both the development of hypothesis-based models and/or hypotheses testing theories. Only such objective evidence can lead to indisputable and validated knowledge (Saunders et al., 2019; Fox, 2008). The basic aim of positivism is the explanation of the co-occurred phenomena under a general law of "constant conjunction" as this explained by David Hume (1739), (Robson, 2009). According to this idea, causality could be inferred only when a) the cause and effect closely co-occur b) the cause occurs before the effect c) and the effect must not occur without the presence of the cause (Field, 2009).

In the context of the present project, a positivistic stance would focus on the systematic identification of predetermined and rule-bound causal relationship between multibehaviours and multimorbidity, which could be generalised, or predicating the outcome of the consultation process between healthcare providers and people with multimorbidity that have engaged with multibehaviours. However, such a strict constant relationship between events is scarce, if not unreal in real world settings (Robson, 2009), particularly when the relationship concerns complex events like multimorbidity or multibehaviours and the combined impact on the patient-healthcare professional relationship. Positivism has been criticised for neglecting the contextual nature of social events (e.g., the primary care settings), failing to acknowledge alternative sources of emerging knowledge, such as the variability of human experience of people with multimorbidity who have had or still being engaged with multibehaviours, and its monolithic stance regarding a value free researcher (Fox, 2008; Banister, 1996).

Interpretivism was the first philosophy to critique positivism. Interpretivism as a philosophical approach emerged from various influences. Such as Gadamer's, ideas on hermeneutics (cited in Regan, 2015), Heidegger's phenomenology 1972 (cited in Schmitt & Richardson, 1966), and symbolic interactionism (Mead, 1972) are the most noticeable ones (Saunder et al. 2019). However, all interpretivist approaches share the idea that social reality is so variable that it cannot be simplified to cause and effect "constant conjunction". Humans relying on their own presumptions, act within diverse social, cultural, and historical contexts and as such construing their personal subjectivity in the interpretation of the social phenomena they are engaged with, resulting in enormous variability of interpretative meanings (Barker, et al. 2002). The main purpose of interpretivism is the better understanding of those meanings. Therefore, humans (consciousness, experience, language) and their artefacts (e.g., texts) are the primary data sources (Robson, 2009). Pursuit of objectivity is rejected and replaced by the plurality that derives from the variety of individual perspectives (Mason, 2002). Consequently, no single universal truth exists outside human cognition and thus multiple realities are inevitable and constantly apparent (Doyle et al. 2009). Axiologically, this means that the researchers must be reflexive of their own meanings that bring into the situation of inquiry while their target is to be able to put themselves in their participants shoes regarding their interpretative point of view (Saunders et al. 2019). In the context of the present project, the target would probably have been to outline the subjective experiences, understanding, meaning and interpretations of people with multimorbidity in relation to their engagement with multibehaviours on issues such as the challenges of living with multimorbidity; their adaptation process and coping mechanisms for managing their situation; and/or their interpretation and engagement with healthcare information and practitioners. However, strong objections could follow the fluidity that accompanies the interpretivist findings that result due the lack of broad applicability, transferability, and/or the identification of possible underlying structures that may contribute to tackling of multimorbidity-multibehaviours phenomenon.

Critical realism aims to unpack the underlying structures of social events, exempt from rigidness of the well-established realism-relativism division between positivism and interpretivism (Banister et al. 1996). By transferring a horizontal division between positivism and interpretivism as it concerns their ontological, epistemological,

axiological assumptions to a vertical one, meaning a mix of the above-mentioned ideas within the same philosophy (Vincent & O'Mahoney, 2018), critical realism manages to present a unified and comprehensive theory (Panhwar et al. 2017). On the one hand, critical realism acknowledges the existence of an external and independent reality (ontology) while on the other it accepts a relativist epistemological stance by introducing a structural formation that the external reality can only be partially observed, resulting in partial knowledge (Guba and Lincoln,2005). Specifically, by distinguishing between the empirical (where only an image of the real events is accessible through sensations and/or observations) and an actual level of reality (where real events occur) a limitation arises where neither our observations nor our knowledge fully capture the external reality (Baskar, 2020). Furthermore, critical realism suggests a separated knowledge a) the intransitive (non-human based knowledge that exist unaltered by human interference) and b) the transitive (changeable knowledge emerged from human social activity) (Baskar, 2008). Based on this assumption, critical realism proposes that while underlying causal laws of reality may still be preserved under controlled environments and closed system that are conditioned to intransitive knowledge, social phenomena that self-evidently are complex, demand the identification of more generative mechanisms able to adapt the transitive knowledge that emerges mainly due to human activity accompanied to social phenomena (Melnikovas, 2018). Thus, interpretative approaches are able to examine open systems, where the "constant conjunction" theorem is not fully applicable, bridging both the ideas of explanation and understanding within the same inquiry (Robson, 2009). In axiological terms this means that a critical realist researcher should be mindful of how the social, cultural, and historical contexts alongside their own personal experiences (the observer effect) might bias their research project. And by acknowledging limitations and bias and taking action to eliminate them, to reach the highest possible level of research objectivity (Panhwar et al. 2017; Vincent & O'Mahoney, 2018). The research paradigm of post-positivism is acknowledged as critical realism's main representative. A "certain pluralism" as described by Panhwar et al. (2017 p.253) in order to denote the technical representation of research that balances between positivistic and interpretivist approaches. In other words, the importance of subjectivity is acknowledged as far as it can support scientifically rigorous methods (Wheeldon & Ahlberg 2014) to objectively examine the majority's experiences (Panhwar et al. 2017).

As such, a critical realist would have approached the present project by focusing on the identification of the most prominent, generalisable relational patterns between multimorbidity and multibehaviours, that affect the majority of multimorbid patients, and the associated impact on their relationships with healthcare professionals.

Despite its more comprehensive research character, some scientists may critique the subjective element's 'supportive' role, expressing additional concerns about the 'imposed' nature of reality stemming from prevailing theoretical frameworks."

Moving beyond the metaphysical debate and seeking justice from “imposed realities” (Hickman, 2007) **pragmatists** depart from the “fruitless” theorisation of truth, as seriously misguided (Noto, 2023). Instead, pragmatists turn their interest to empiricism and the practical consequences of ideas to the real world (Wills & Lake, 2016). They argue that ignoring human experience has led scientific inquiry to pursue answers to the wrong questions (Morgan, 2014). For that reason, pragmatists propose a philosophical approach inextricably linked to human experience (Hartman, 2003). Experiential “truth” is assessed by the effectiveness of abstract ideas to establish beliefs as a “consequence” of successfully addressing an inquiry or a problematic situation that requires a practical solution (Sanders et al. 2019). As Patten, (1911, p. 660) stated “consequences as the ultimate test of truth”. For pragmatists, methodology supersedes ontology in the pursuit of knowledge, treating knowledge as synonymous to inquiry (Morgan, 2014). Research questions are the cornerstone of pragmatic epistemology provoking the implementation of action-oriented ideas (research designs), able to bring a temporal equilibrium, between actions/applied methods, experiences/outcomes, and beliefs/new concepts within an unbalanced real-world foreground (Wills & Lake, 2016). The temporal dimension refers to the dynamic evolution of knowledge, while the equilibrium denotes its evaluative character and its ability to effectively address real-world problems (Sanders et al. 2019). In other words, inquiry is a contextually determined, self-conscious, moral (what is ethically right or wrong), political (related to exertion of governance/power) and value-laden (focus on what is important) decision-making process, fulfilled via experimentation and problem-solving (Denzin, 2010). Consequently, a pragmatic researcher must be value driven and reflexive about both the interpretive nature of experience (how beliefs are interpreted to provoke action, and/or how actions as outcomes, are interpreted to emerge beliefs) and the historical, cultural, and social

contextuality of the inquiry (since even our most personal thoughts are social constructed) (Morgan, 2014).

Thus, a pragmatic approach to the current project would prioritise the practical implications of research findings for improving healthcare and the healing relationships. For that reason, the focus would have turned to the analysis of medical records where via statistical analysis the exploration of patterns and prevalences rates of multimorbidity and multibehaviours of a specific population would probably be identified. Furthermore, via interviews the pragmatic researcher would be interested to explore the consequences of multimorbidity patterns to the lived experiences, and perceptions of both healthcare providers and people with multimorbidity that still engage with multibehaviours alongside the contextual influences (healthcare setting, family, area of living etc.) and their practical implications always already to suggest needed reformations.

A similar focus toward the experiential, and political emergence of knowledge, though more intensely pursuit, is also postulated by **post-modernism**. This approach pursues an assembly of related systems of beliefs and assumptions that stands sceptical and critically against any type, form, or level of dogmatic assumptions or otherwise “grand narratives” (Lyotard, 1979) that govern currently societal systems like science, sex, race, healthcare, education, and government (Melungeons & West 2016). As such no better definition could be applied for post modernism apart from the one that compares it with modernism ideas. As Clarke (2018 p.9) state, “If modernism emphasised universality, generalisation, simplification, permanence, stability, wholeness, rationality, homogeneity, and sufficiency, the post-modernism shifted emphases to partialities, positionalities, complications, tenuousness, instabilities, irregularities, contradictions, heterogeneities, situatedness and fragmentation – in all their methodologically challenging glory”. Ontologically post modernists see the world as highly fragmented, a patchwork of multiple realities conditioned to power exchange (Parker & Chan, 2000). Epistemologically, they are particularly inclined to examine how language and power usage produce knowledge that afterwards is used by grant narratives (worldview shared by majority) to oppressively provide a homogenous fictitious version of reality, social thinking, and action (Ellaway, 2020). For that reason, “biasing” toward small narratives the major epistemological goal of post modernism is the identification of those

underlying structures and discourses that support an alternative explanation. In axiological terms, this means that the researcher has to be reflexive and responsible for the kind of knowledge produced, alongside its historical, moral, and political perspectives. In other words, "Who is authorised and not authorised to make what kinds of knowledge claims about whom/what, and under what conditions?" (Clark et al., 2018 p.10). In that sense a postmodernist researcher can act in double critique manner, questioning not only traditional views but also the motives and perspectives of those who are challenging or redefining truth in new ways (Ellaway, 2020), in effort to generate knowledge that contribute to making of a better world (Clarke et al. 2018).

Thus, a post-modernist approach would primarily focus on deconstruction of the grand narratives of "multimorbidity" and "multibehaviours" as socially constructed ideas and how these have shaped our understanding about health. Furthermore, by fostering a participatory research design, where participants could actively contribute to shaping the research process, the post-modernist researcher would prioritise the identification of power imbalances within the healing relationship, analyse how the broader socio-cultural and political factors might influence the individual experience of participants and researcher, as well as the interpretation of data collected.

2.2.1.2 Approach to theory development

This second level of outer layers regards with the manner in which eligible knowledge emerges. The decisions taken in this stage are linked to those of the previous stage as they will, in turn, influence subsequent decisions regarding research design (Awuzie & McDermott 2017). According to Sanders et al. (2019) three reasoning approaches, namely deductive (theory testing), inductive (theory building), and abductive (suggested development of new or existed theory) are of concern here.

The deductive approach is regarded a top-down analytical process that seeks to verify or disprove a pre-existing hypothesis or theory (Soiferman, 2010; Azungah, 2018) in effort to support the generalisability of pre-existed evidence (Wheeldon & Ahlberg, 2014). As such, it is usually linked with positivist methodologies (Thompson, 2022). However, due to the preconceptions that accompany the procedures of deductive data

collection and analysis, concealments and/or omissions on pivotal aspects of the inquiry are largely expected (Thomas, 2003).

On the opposite side, the inductive approach is a bottom-up exploratory process that aims to establish a generic and/or theory building assumptions via interpretative methods to examine participants' perceptions (Wheeldon & Ahlberg, 2014; Thompson, 2022). This is accomplished through a step-by-step process that prevents researcher's pre-existing influences to affect the final outcomes (Azungah, 2018). Induction is usually used when previous theoretical assumptions are limited or a better understanding of complex data is prerequisite (Thomas, 2003), though with the cost of emerging a 'new' theory based on limited observations' (Conaty, 2021).

Neither the inductively emerging new information (as it is merely a description of the already observed patterns in raw data) nor, the deductive validation of the already existing theoretical assumptions could be regarded as a genuine new knowledge (Haig, 2023). Therefore, the literature suggests that researchers often struggle to choose between inductive and deductive approaches when trying to establish a theory-research link, especially when this comes to combining research approaches for testing or developing theories within the framework of a specific study (Awuzie & McDermott 2017).

The abduction approach has been suggested as a way to fill this gap (Awuzie & McDermott 2017) due to the judgmental character of its explanatory factors regarding the validity of research hypotheses and theories (Haig, 2021). Grounded on pragmatism, abduction balances empirical data with the researcher's current understanding of the theory (Thompson, 2022). This means that the researcher does not approach the research inquiry as "tabula rasa", but rather as intermediator of the pre-existing theoretical knowledge. This knowledge serves as the backdrop, setting boundaries that influence what the research aims to reveal. However, since abduction avoids being solely theory or data driven, researchers avoid both to be obliged to fit empirical data into established theoretical understanding or to uncover abstract and arbitrary results not relevant to the research question (Alvesson & Kärreman, 2007; Coffey & Atkinson, 1996). While by, moving back and forth between known facts and new intuitive possible explanations (Aliseda 2007) it permits the emergence of genuine knowledge (Awuzie & McDermott 2017).

2.2.2 Intermediate layers of the Research Onion model

The next decisional level of the research onion model regards the three intermediate layers that are related with the practicalities of the research design and encompass the methodological choices, research strategy and time horizon issues.

2.2.2.1 Methodological choices

This layer refers to the application of three main research designs namely the qualitative, quantitative, or mixed methods (Dissanayake, 2023). Research designs could be mono-method (when one technique is applied), poly-method (when multiple techniques, though within the same research design implemented) and or mixed-method (when both quantitative and qualitative techniques employed) (Tengil, 2020).

Three main characteristics may signify the usage of a particular research design. Firstly, the idea that specific designs act as a rule of thumb for specific research inquiries (Soiferman, 2010), despite the fact that no evidence exists for direct, normative connection between methods, methodologies paradigms (Symonds & Gorard, 2010). For example, closed research questions usually leads to the implementation of fixed research designs that used to collect and analyse quantitative data (Robson, 20160). Secondly the differences in language usage with those follow the quantitative approach to screen out any form of interpretation in favour of "unmediated representation of the object of study" (Banister et al. 1996, p.2), something that qualitative researchers disagree with and so embrace interpretation as the crux of the qualitative research designs (Banister et al. 1996). Thirdly, the stance of researcher towards the study's participants such as the value-free stance of quantitative researcher that indicate the focus on "variables" outside the participants' personal characteristics and in contrast, the reflexive stance of their qualitative counterparts as indication of the awareness of the interrelationship between the researcher and the participants in understanding the researched inquiry (Soiferman, 2010).

Regarding aim of the research design, quantitative research is usually related with deductive testing of theories (Rana, et al. 2020), qualitative research with the inductive development of theories (Soiferman, 2010), while abduction is more focused on the

rigorous establishment of researchers' intuition theoretically and empirically (Wheeldon & Ahlberg, 2014).

In the specifics quantitative research, basing on predefined protocols and procedures involves collection and analysis of numerical data to address scientific research questions. This dictates the reduction of phenomena to numerical values for statistical analysis, emphasising the significance of variables in classification and quantification (Field, 2009). As such, it draws on variables that produce numeric outcomes and, by employing statistical techniques, it can provide summaries, averages, identify patterns, make predictions, test causal associations, and provide evidence for theories that can be generalised to broader populations (Apuke, 2017). Thus, quantitative research has been criticised for overlooking the role of setting and context, as well as its heavy reliance on statistics. Qualitative researchers criticise the quantitative counterparts overemphasis on the statistical significance of 'average' as this systematically overlooks the participants perceptions of the phenomena under investigation and as such the complexities that accompany their behaviours (Wheeldon & Ahlberg, 2014).

Qualitative research is a study conducted in a natural setting with a flexible design that unfolds the inquiry as the research progresses (Soiferman, 2010; Robson). In contrast to quantitative research designs, qualitative researchers are not trying to be value-free but consider themselves as playing a central role in interpretation of a problem under investigation (Banister et al. 1996). In this sense, qualitative research is regarded as an interpretive procedure where the researcher scrutinises participants' meanings and understandings to develop via their interpretations related theories (Thompson, 2022). The goal for a qualitative researcher is to work in a systematic and inductive way for the analysis of data to go beyond the simple presentation of participants narratives; it aims to transform raw data into meaningful 'new' information/theory through summarising, synthesising, and restructuring (Thomas, 2003). This enables readers to comprehend though the individuals' experiences and perceptions both theoretical and practical implications of the inquiry under investigation (Thompson, 2022; Wheeldon & Ahlberg, 2014). Finally, by acknowledging their own participation and biases in research outcomes, qualitative researchers not only emphasise the importance of personal perspectives and multiple realities, but it also challenge the notion of objectivity assumed within quantitative approaches (Wheeldon & Ahlberg, 2014).

Mixed methods are a methodological response to inefficiencies of quantitative and qualitative approaches to meet the contemporary complex needs of modern scientific inquiry by depending solely on their own (Symonds & Gorard, 2010). By promoting an inclusive methodology, where both quantitative and qualitative methodological qualities are considered, mixed methods reject the “false dichotomy” incompatibility thesis of methodological “purists” (Sandelowski, 2001) on the premise that the merging of ontological and/or epistemological perspectives is not viable (Cuba & Lincoln, 2005). As it is argued, both statistical and qualitative analyses are subject to some form of personal judgement and interpretation (Gorard, 2006). Thus, mixed method researchers that multi-faceted research problems common in social healthcare research can be better addressed through a comprehensive mixed methods approach (Wheeldon & Ahlberg, 2014). The main rationales for choosing mixed methods research design include:

- Methodological triangulation provided by the agreement of between quantitative-qualitative study outcomes that eventually enhances projects validity.
- Holistic view of inquiry under investigation that enhances collaboration between various disciplines
- Focusing on strengths of each methodological approach (qual.-quant.) eliminating their weaknesses).
- Flexibility to address larger variety of research questions
- Better able to provide practical solution encouraging the exploitation of multiple worldviews and methods
- Development and testing of novel hypotheses (Doyle et al. 2009; Morgan, 2017).

The successful integration of quantitative and qualitative approaches under the unified umbrella of mixed method research project led many to consider mixed methods as "the third methodological movement" (Symonds & Gorard, 2010) and furthermore to be backed up by philosophical assumptions (Tashakkori& Teddlie 2003). Some argue that this development, instead of reconciling methodologies, leads to a third incompatible position among them (Symonds & Gorard, 2010). Yet it seems that where research is philosophically rooted plays a considerable role. For example, while it is true that mixed methods research designs can include both pragmatism and post-positivism philosophical assumptions (since the latter is rooted in critical realism), it could also be

argued that post-positivism still relies heavily on quantification, and using qualitative methods simply offers supportive evidence to that emerged from statistical analyses data. Consequently, post-positivism exploits only a limited version of mixed method's potential.

On the contrary, pragmatism emphasises practicality, flexibility, and methodological pluralism, which can allow better navigation of complexities with mixed methods research designs than post-positivism (Creswell & Plano, 2017). For example, by embracing abduction thinking, pragmatism approach allows the back and forth between induction and deduction thinking allowing researchers to exploit the strengths of either quantitative or qualitative methods, minimising their weaknesses (Morgan, 2017). In turn, this can permit the emergence of new knowledge beyond the reach of singular traditional methodologies (Wheeldon & Ahlberg, 2014). For that reason, mixed methods have become a dominant research design in contemporary healthcare projects (Doyle et al. 2009; Brannen, 2005; Wheeldon & Ahlberg, 2014).

A final point on mixed methods and one of the most controversial issues (Morgan, 2017) regards with the variety of typologies that mixed theorists have developed to describe the numerous ways that qualitative and quantitative methods can appear in a single research project. The importance of the matter lies in the premise that a classification system for mixed methods is helpful because it makes the research process more thorough, gives direction, and helps to create a language for talking about mixed methods research (Doyle et al. 2009). The most common typologies are summarised.

Morse & Niehaus (2009) typology, (*cited in* Morgan, 2017), upgraded the primary typology ideas of Morgan's (1998) system. Within their typology both temporality (referring to the time sequence of methods usually congruent or sequential) and weighing (regarding with the priority of method in relation to research question) parameters are considered, in addition to the theoretical orientation of the study (e.g., induction, deduction). Importantly method emphasis is denoted by upper case for the primary method and lower case for the complementary method. Sequencing of each method relative to the other is indicated by an arrow (see Table 1). Accordingly, Creswell & Planko Clark (2011) within their typology (*cited in* Morgan, 2017), integrating the weighing and temporal elements of the previously mentioned typology regarding the

parallel or independent chronological arrangement of datasets analysis they add six distinct designs:

- embedded design - involves the integration of qualitative and quantitative approaches to gain deeper insight
- convergence design - involves the simultaneous collection and merging of quantitative and qualitative data to address the research objectives
- sequential designs - involves the building of one dataset (e.g., quantitative) on the emerging results of another (e.g., qualitative)
- Multiphase design – results derived from longitudinal multiple projects interrelated in common target, and involves elements from both convergent and sequential designs where phases are conducted sequentially with each one building on the results achieved from the previous one.

Table 1. Morse and Niehaus's (2009) Eight Design Types

Design	Theoretical Orientation	Timing
QUAL → quan	Inductive	Sequential
QUAL → qual		
QUAN → qual	Deductive	
QUAN → quan		
QUAL + quan	Inductive	Simultaneous
QUAL + qual		
QUAN + qual	Deductive	
QUAN + quan		

2.2.2.2 Research strategy and time horizon issues

The last two phases in the intermediate decisional level focus on research strategy meaning the applied form of research. For example:

- Experiments where research involved a great control over environment and an active manipulation of cause variable(s) anticipating a specific effect on the outcome one (Field, 2009).
- Survey, where collecting information from a sample of population provides quantifiable responses to specific questions" (Rana et al. 2021).
- Case study, where research involves a thorough and intensive investigation of a social unit (e.g., person, organisation, culture) in real life settings (Kothari, 2004)

- Ethnography where a cultural group is studied in its natural setting over a period of time (Robson, , 2009)
- Action research, where researcher's methodological investigation aimed to tackle real world inquiry by attempting to provide positive change solutions (Robson, 2009)
- Grounded theory (the inductively generated theory of social processes grounded on the views of the participants (Clarke et al. 2018)
- Narrative inquiry where researcher bases its inquiry on the provision of participants' related story telling (Tengil, 2020) and whether chosen study's design is going to be either
- cross sectional meaning that data is collected at a single point in time or brief period of time and/or
- longitudinal meaning that data is collected at several points in time and for prolonging period (Robson, 2009)

2.2.3 Inner layers of the Research Onion model

This is the final decision level of the inner layer (Saunders et al. 2019) where the tools and methods used for gathering information, such as scales, questionnaires, and interviews. It also concerns the presentation of the study area, explaining why the specific location was chosen, further supported by information on the study population and the sampling procedures.

2.3 Application of the Research Onion model in current study

2.3.1 The Pragmatic phase

The primary goal of adopting a pragmatic philosophy in this project is to yield tangible research outcomes aiming at improving the provision of healthcare to people with multimorbidity and supporting better and more functional healing relationships between healthcare providers and people with multimorbidity. As a result, the pragmatic phase of the project is directed towards conducting an extensive analysis of medical records, employing statistical methodologies to identify prevalent patterns and prevalence rates of multimorbidity and multibehaviours within a defined population.

Consequently, this pragmatic phase encompasses specific quantitative studies aimed at achieving these objectives.

2.3.1.1 Systematic Review Meta-analysis

The first step for answering the project's research question started with the implementation of a systematic review and meta-analysis regarding with the effect of multibehaviours on multimorbidity risk. In other words, the provision of a standardised synthesis of literature on analytical research evidence derived from all included single observational epidemiological studies that met specific criteria (Dickersin, 2002). Where possible, the studies statistically estimated the aggregated outcome effect of multibehaviours on the development of multimorbidity (Thacker, 1988). The rationale for implementing a systematic review – meta-analysis was related with the great variability that exist between single study effect estimates (Petticrew & Roberts, 2006) and the practical need for both minimising erroneous understanding (Moher et al., 2009) and supporting evidence-based clinical decisions.

To reach this milestone, a systematic review meta-analysis follows a bibliographic 'experiment'-like methodology which served to minimise bias via transparency, replicability, and employability of strict standards (Dickersin, 2002), while trying to identify, critically assess, and integrate all the relevant literature on a specific inquiry (Cronin, 2008; Denison et al. 2013).

This effort towards a rigorous and comprehensive examination of all available evidence on a specific question makes systematic review - metanalysis an invaluable research tool within healthcare inquiry (Petticrew & Roberts, 2006), considered by many to be at the top of evidence hierarchy (Haidich, 2014). Thus, systematic reviews – metanalyses serve various theoretical and practical goals ranging from helping healthcare professionals to stay up to contemporary field's developments (Petticrew & Roberts, 2006) or to support decision making to even research uncharted territories of otherwise well and wide-ranged inquiries and thus influencing future research (Moher et al., 2009). These goals were aimed to be served by the current systematic review and meta-analysis. The results of systematic reviews-metanalysis of aetiological observational studies like this one, hold great significance for public health practitioners and policymakers. Even a slight increase

in the likelihood of identified causal linkage, can have a significant impact on public health particularly when exposures, like the SNAP multibehaviours that were examined by the current PhD project (Chapter 4) (Dickersin, 2002; Stroup et al. 2000).

To summarise, systematic reviews can act as challengers to those who control a "crystalised" knowledge (e.g., experts, schools of thoughts, paradigm's orthodoxy) of "how", "when", and "if" a study with particular results is publishable (Petticrew & Roberts, 2006).

Four main questions can be answered by a systematic review – metanalysis as argued by Higgins & Greene (2009, p.244)

- What is the direction of effect?
- What is the size of effect?
- Is the effect consistent across studies?
- What is the strength of evidence for the effect

The first three are usually answered by the narrative synthesis of included studies results and only the last one is indeed dealt with by meta-analysis whenever possible.

However, performing metanalysis is still debated among the scholars mainly due to innate design fallacies of the primary observational studies (e.g., uncontrolled confounding). A counterargument stresses that judging the meta-analytic outcome by the design of the study is somewhat inappropriate as it ignores the study quality; e.g., accepting a badly designed randomised control trial study and rejecting a well-implemented observational cohort study (Borenstein et al. 2009). Thus, despite the challenges in estimating aggregate effects outcome and dealing with researcher's decisions that accompanied this task (Higgins & Green, 2009) the pursuit for metanalytic evidence from observational studies should continue. This should be undertaken with cautious and well-defined methodological and analytical steps, acknowledging the limitations but also the importance of the task. Nevertheless, it is important to remember that some inquiries cannot be addressed through randomised control trials and require evidence from observational studies (e.g., where random allocation, blinding and other RCT design features are not feasible or unethical) (Borenstein et al. 2009).

One such systematic review-metanalysis is the present one, which had a broad scope to overcome the focus on a single comparison. Specifically, the first concern was the identification and collation of studies of whether multiple exposure on health risk behaviour is associated with Multimorbidity, and aimed to identify the existence of dose response association between two, three, four SNAP multibehaviours and multimorbidity risk. While 'upgrading' reviews by implementing metanalysis, it was crucial (as with every other analysis) to have a reflective approach in constructing both the narrative and quantitative parts, for example, when making decisions around which comparisons to include in meta-analyses.

Thus, for securing the integrity of scientific process and the present systematic review-metanalysis followed a predefined protocol and methodology according to PRISMA (Dalgleish et al. 2007; Haidich, 2014) and Cochrane's Collaboration (Higgins & Green, 2009) regulations that are both presented in more detail Chapter 3 Methods section of the specific systematic review-metanalysis.

To summarise, the developing and registering the review protocol ensured that the decisions taken during the review reflected those made prior to its implementation regarding the specific hypothesis, the sampling strategy and/or the PICO (population, intervention, comparison, and outcome) inclusion/exclusion criteria as well as other issues (e.g., data collection). All these decisions affected the final study. This also promoted transparency and replicability (Greenberg et al. 2005; Higgins & Green, 2009).

2.3.1.2 Epidemiological studies

The next pragmatic step toward answering main project's question regarded implementation of a multifaceted, multicentre epidemiological study to interrogate further the association between multimorbidity and multibehaviours. Like every epidemiological study, the present one addressed issues that contribute to the development of morbidities broader than the biological ones that are usually the focus of medical research (Greenberg et al. 2005). The epidemiological studies are divided to descriptive and the analytic studies. While the focus of the first regards with the presentation of the frequency distribution of health events to the population the later are mainly concerned with the identification of possible determinants of those health

events (Greenberg et al. 2005). Therefore, the design of the current project had an analytical character basing on the assumption that health phenomena such as multimorbidities do not arise randomly to population but rather the occur by the assemblage of risk factors(Fisher & Ma, 2014). Thus, the main purpose of the study was to investigate the patterns and distribution of multimorbidity (the health-related event under investigation) as those determined after its association with multibehaviours within the registers of the three participating GP practices (specific population). To do that a fundamental aspect is to be able to quantify the association between multimorbidity and multibehaviours. This required a comparison group (Bonita et al. 2006; Jewell 2009), which in this case, was registers of the participating GP practices' with none or one chronic condition.

Due to the nature of a study an observational correlation design was implemented (Robson & Mc Cartan, 2016). This was appropriate because it would be unethical to experimentally manipulate the SNAP multibehaviours, and it was not feasible to implement a longitudinal cohort design with disease outcomes (Rosenbaum, 2021). The chosen cross-sectional design was feasible, flexible, and allowed a "snapshot" of exposure (multibehaviours) and the health phenomenon (multimorbidity) (Priestly, 2012). The underlying assumption was that the study population is assumed to be exposed to risk factors for sufficient time for outcomes to manifest and will continue to be exposed in the absence of an intervention (Grimes & Schulz, 2002).

However, the main drawback of the cross-sectional design is the inability to infer causality because of the simultaneous examination of both exposure(s) and health phenomenon. It is also impossible to eliminate a threat of possible contamination of the observed correlation from a hiddenly influential variable (confounding) or the possibility of the existence of systematic errors (bias) either during to the collection of participants (selection bias), or their misplacement (misclassification) (Wartenberg & Scholar, 2006). These problems, such as confounding has been suggested to be solved via statistical analysis e.g., by stratifying the sample and adjust statistical analysis for particular characteristics like age, sex, and socio-economic status. More details about this are presented in Chapter 4 and particularly at Methods and Results sections.

2.3.2 The interpretive turn to Post modernism approach and Situational Analysis

The interpretive turn signifies the inclusion of postmodern ideas into the project's pragmatism. This is primarily based on the premise that multimorbidity and multibehaviours are two interconnected social phenomena that, nonetheless, remain deeply embedded in the dynamics of our social world. Thus, as Rabinow & Sullivan have argued, the necessity for an interpretive turn is rooted in "the realisation that all human inquiry is necessarily emerges from an understanding of the human world within a specific situation, which is simultaneously historical, moral, and political…" (Clarke et al. 2018, p.9). In short, this interpretive turn signifies the introduction of postmodernist theories, specifically those related to power imbalances, particularly as they pertain to the key issue of the nature of knowledge and who possesses it.

The interpretive turn of the present project is marked by the implementation of a research method called Situational Analysis (Clarke, 2005) that balances between pragmatism and post modernism. While rooted to a pragmatically inspired Grounded theory, Situational Analysis introduced a different "conceptual infrastructure and guiding metaphor" (Clarke, 2003 p. xxiv), shifting the focus from the social processes to situation of inquiry itself embracing every form of complexity arises from it (Clarke et al. 2018). Situational Analysis also differentiates from the previous approach of Grounded Theory, which aimed to construct broad, generalisable narratives about the fundamental social processes behind a phenomenon. Instead, Situational Analysis proposed a different methodological approach centred on understanding situations, capable of providing a detailed analysis of all elements—human and non-human—that are intertwined within complex social contexts through a conceptual framework likened to map-making. This in-depth analysis surpasses the perspective of the observer and recognises the potential for alternative outcomes. The primary goal of the project was to thoroughly explore the intricate social dynamics of a specific situation and develop reflective and insightful theoretical assumptions regarding the interplay and impact of medical (multimorbidity) and behavioural (multibehaviours) complexities on the interactions between healthcare providers and patients with multimorbidity, whether together or separately.

In practice, Situational Analysis is implemented via a three-step iterative process, where each phase informs and is influenced by the others. There are fluid boundaries between

these analytical stages, with data collection and analysis in each phase being shaped by the findings of the preceding ones. This iterative process continues until a saturation of evidence is achieved. Continuous memoing and thorough review of the data helped the researcher overcome biases and preconceptions derived from existing qualitative literature. The ultimate outcome consists of three sets of conceptual maps (situational maps, social worlds/arena maps, positional maps) that illustrate the intricate interconnections and complex structures of multimorbidity and multibehaviours, both among themselves and with other factors contributing to the complexity of the situation under study. The three phases of Situational Analysis included:

- Situational maps, which encompassed messy, ordered, and relational maps, examining all significant human and non-human elements of the investigated situation.
- Social worlds/arenas maps, which analysed all collective actors (humans) and actants (non-humans) in relation to the arena where they interacted and negotiated discourse related to the situation.
- Positional maps, which depicted all positions (taken and not taken) arising from data regarding key discourses, concerns, or major controversies surrounding the investigated situation.

At the end the outcome of Situational Analysis will be a “thick analysis”, goes beyond the “knowing subject” that acknowledges “that things could be otherwise” revealing the social of the situation something that usually missed by qualitative research (Clarke et al. 2018).

2.4 Summary of methodology

Summarising, to provide a pragmatic answer to objectives set in section 1.12, regarding the multimorbidity and multibehaviours, the current project implemented a mixed method approach as its driving force. In this effort, the research paradigm, along with methods of data collection, analysis, and ethical considerations, have been thoroughly considered to align with the nature of the study. Detailed descriptions of the specific methods, processes, and procedures can be found in their respective chapters.

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After detailing the methodology followed by the present thesis, the following chapter introduces the first applied study of the project, focusing on investigating the association between multimorbidity and multibehaviours within published literature.

3. Exploring the Interplay: Multimorbidity and Multibehaviour - A Systematic Review and Meta-Analysis

3.1 Background

Evidence derived from clinical-epidemiological medicine and research, indicates that the co-existence of non-communicable diseases, or multimorbidity, is an incrementally prevailing phenomenon (Violán et al. 2014; Abad-Díez et al. 2014). Multimorbidity, though more frequent in older ages (Marengonni et al. 2011; Fortin et al., 2014) due to demographic transition toward an older population (Gijsen et al. 2001; Van Den Akker et al. 2000), is observed in all adult groups (Jakoviljevic & Ostjic, 2013). In actual numbers, the majority of people with multimorbidity are of working age and certainly under 65 years old (Barnet et al. 2012). Multimorbidity is prevailing amongst chronic disease patients (Barnett et al. 2012; Wang et al. 2014) complicating the treatment burden for both people with multimorbidity (Shadmi, 2013) and their healthcare providers formal (Salisbury et al. 2018) and informal ones (Lindvall et al. 2016).

Multimorbidity's impact extents from individual to societal level (Willadsen et al. 2016). Decreased functional capacity (Marengoni et al. 2011; Afshar et al. 2015) and quality of life (Fortin et al. 2004) followed by an increased risk of health complications (Salisbury et al. 2011), polypharmacy (Doos et al. 2014), psychological distress (Prados-Torres et al. 2014), excessive health care use (Van Oostrom et al. 2014; Glynn et al.2011) and costs (Vogeli et al. 2007) are all multimorbidity's consequences on patients' health status and daily life (Diederichs, et al. 2012). Equally pressing, the sex and social patterning that follows the multimorbidity with women and those in most deprived areas to be most prevalent (Violán et al., 2014). Indicatively, a study in UK has shown a gap in the onset of multimorbidity of 10-15 years between those from deprived areas to those from the most affluent (Barnett et al. 2012). Thus, researchers seeking aetiological evidence on key determinants of chronic conditions (Agborsangaya et al. 2012; Gijsen et al. 2001; Kim et al. 2013; Wilksrom et al. 2015) (i.e., health risk/enhancing behaviours) in order to prevent (Violan et al. 2014) or tackle multimorbidity's prevalence (Jakoclević & Ostojić, 2013), and worsening trajectory (Katikireddi et al. 2017).

Health behaviours are defined as any behaviours that influence health in a deteriorating or preventative manner (Ogden, 2007). The four most common health behaviours are

smoking, nutrition, alcohol consumption and physical activity (SNAP) (Prochaska, Spring, & Nigg, 2008). Similar to multimorbidity, health risk behaviours tend to co-exist, creating multiple risk behaviour patterns (Meader et al.2016). These multibehaviours are also common in adult populations, with one study showing that just 3% of the population seem to fully comply with the healthy guidelines concerning the four SNAP behaviours (Prochaska, 2008).

Although, the multimorbidity-SNAP health risk behaviours association has only recently been thoroughly investigated (Marengoni et al. 2001; Violan et al. 2014), numerous studies (Luben et al. 2020; Schäfer et al. 2019; Zacarias-Pons et al. 2021; Jackson et al. 2016; Wikstrom et al. 2015) have shown that the specific modifiable lifestyles factors (Jackson et al. 2016; Wang et al. 2014) can be conceptualised as precursors of multimorbidity (Afshar et al. 2015). Studies that examined their combined effect reported stronger associations than those exploring single health risk behaviours (Loprinzi, 2015; Dhalwani et al. 2017).

The literature suggests a social patterning in both multimorbidity-multibehaviours (Salisbury et al. 2011; Barnett et al. 2012; Allen et al. 2017), that increases health inequalities by disproportionately worsening the health outcomes of socially disadvantaged groups (Khlat et al. 2004; Stockings et al. 2013; Violán et al. 2014; Abad-Díez et al. 2014), which adds more complexity to situation.

Generally, healthcare systems worldwide have been designed to effectively treat single conditions based on rigorous single-disease based guidelines (Hughes et al. 2013; Nolte et al. 2008). As such the complexity derived from the multimorbidity-multibehaviours relationship has posed considerable challenges to these single disease-based health care systems (Barnett et al. 2012; Padros-Torres et al. 2014). The consequences of reactive and fragmented responses from both preventative (Prochaska, 2008) and clinical medicine (Stumm et al. 2019) include multiple healthcare burden (Shadmi, 2013)and increased risk of medical complications (Mercer et al. 2016), development of ineffective preventive services (Violan et al., 2014), and increased numbers of patients with multiple health care needs that receive sub-optimal care (Agborsangaya et al., 2012) which is detrimental for the progression of their treatment (Sinnige at al., 2013).

Part of this confusion derives from the lack of an agreed multimorbidity operational definition. In an effort to accurately estimate multimorbidity prevalence, numerous

indices have been applied (Buffel du Vaure et al. 2016), including the Charlson Comorbidity Index, the Chronic Disease Score, the RxRisk Model, and the Duke Severity of Illness Checklist, among others (Fortin et al. 2012; Sinnige et al. 2013). However, these indices contribute to further heterogeneity within specific inquiries. Simply put, some indices perform better in certain domains. For example, the Adjusted Clinical Group (ACG) is more suitable for assessing hospital stays, while the Cumulative Illness Rating Scale is better for classifying morbidities within particular body systems (Diederichs et al., 2011).

Despite growing evidence to support further investigation of the multimorbidity-multibehaviours relationship (NICE, 2016; Katikireddi et al., 2017), to the researcher's knowledge, no study has examined the pooled effect of this association. The main aim of this review was to provide meta-analytic evidence on multimorbidity-multibehaviours association, by quantifying their association. Such evidence should help to advance both theoretical and clinical knowledge, shifting scientific inquiry toward a better integrated multimorbidity-multibehaviours healthcare framework (Loprinzi, 2015).

3.2 Methods

The current review followed a protocol (Appendix 1) registered on Prospero (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018111026) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and is reported in accordance with the Cochrane Collaboration methodology (Higgins & Green, 2009).

3.2.1 Inclusion criteria

Both cross-sectional and cohort non-randomised study designs were eligible for inclusion if they investigated the combined effect of exposure to at least two of the four most common health behaviours of smoking, nutrition, alcohol, and physical activity (SNAP), on multimorbidity risk and comprised adult participants (aged ≥18 years) from the general population or primary care settings.

For the primary outcomes, all forms of multimorbidity indices were considered, from simple counts (MM2+, MM3+) to measures of cumulative indices including Quality and

Outcomes Framework (QOF), Adjusted Clinical Group (ACG) system, Charlson Index, Cumulative Index Illness Rating Scale (CIRS), Chronic disease score (CDS), Duke severity of illness checklist (DUSOI). Two secondary outcomes, that were not included in the preregistered protocol, were also considered for exploratory reasons: the pooled effects of specific clusters of health risk behaviours on the development of multimorbidity; the effect of SNAP multibehaviours on social patterning of multimorbidity.

3.2.2 Search methods for identification of studies

We applied the search strategy (Appendix 2) to five electronic databases (MEDLINE, Scopus, PubMed, CINAHL and PsycINFO) and followed a snowball method using the reference lists of included articles to identify other potentially eligible studies.

Since multimorbidity is a relatively new term that was not frequently used in articles before the 1990s, in keeping with other reviews (Ryan et al. 2015; Sinnige et al. 2013; Smith et al. 2012), the search was limited to articles published from 1990 to 2021.

Medical Subject Heading (MeSH) terms were used, including “Comorbidity”, “Diet”, “Fruit”, “Vegetables”, “Exercise”, “Leisure activities”, “Sedentary lifestyle”, “Smoking”, “Alcohol drinking”, alongside keyword(s) that referred a) to multimorbidity (e.g., multiple diseases, multiple conditions, multiple long-term disease, concomitant diseases or multiple non-communicable disease) and b) health risk/enhancing behaviours (e.g., healthy/unhealthy diet, physical (in)activity, tobacco smoking, and alcohol abuse or excessive drinking.

Other refinements were made to filter the search results:

- Only studies that examined the combined effect of two or more SNAP health behaviours (multibehaviours) on the development of non-communicable multimorbidity were included.
- Studies that exclusively examined multimorbidity in relation to mental illnesses, were excluded.
- Cancer survivors were treated as chronic patients only if their survivorship exceeded five years from initial diagnosis.

- Smoking, alcohol, diet, and physical activity were treated as health behaviours, even when studies had examined them in the context of addiction (e.g., alcohol addiction).
- Obesity was treated as chronic condition-risk factor, rather than a health risk behaviour.
- Randomised Control Trials (RCT) were included only when the control group(s) had zero or one chronic condition.
- Only English Language articles were included.

3.2.3 Data collection and analysis

The principal researcher (KS) conducted the preliminary screening of titles and abstracts as well as the extraction of the relevant information from the final included studies. One supervisor (CG) acted as a second reviewer verifying the quality of screening and data extraction, with another supervisor (NE) resolving any discrepancies.

3.2.4 Data extraction and management

Data extraction was performed using the Cochrane Collaboration data collection form of Effective Practice and Organisation of Care (EPOC) (Higgins & Green, 2009). The following information was extracted: study and participant characteristics (design, settings, eligible population, sociodemographic characteristics); specificities of study design; processes such as recruitment method, duration of participation and follow up period; types of exposure and multimorbidity measurement; presenting results; type of outcomes; and stratification and adjustment methodologies against confounding and/or missing data.

3.2.5 Assessment of risk of bias

For the assessment of internal validity of the included articles, study quality assessment was treated separately from risk of bias assessment as even high-quality studies can be prone to significant risk of bias (Higgins & Green, 2009).

The pilot tool, ROBINS-E (Appendix 3), a specialised version of ROBINS-I for non-randomised intervention studies was chosen. This tool is more suited to identify possible

sources of bias with epidemiological exposure studies compared with ROBINS-I, which is more focused on interventions (Sterne et al. 2016).

3.2.6 Data analysis

A narrative synthesis of study and participant characteristics (i.e., socio-demographic, population, settings, country, and year of publication) and outcomes was used for those that could not be statistically analysed. Otherwise, overall, and stratified meta-analyses were performed on at least two outcomes. Random-effects meta-analysis was used to examine the overall effect of health risk behaviours effect to multimorbidity risk given the expected clinical and methodological heterogeneity between studies in relation to participant age, the morbidities used to measure multimorbidity and/or the number of health risk behaviours investigated, (Higgins & Green, 2009). Heterogeneity was statistically examined via Chi^2 test and I^2 statistic thresholds to classify heterogeneity as moderate (30%-60%), substantial (50%-90%), or considerable (90%-100%). Specifically, the I^2 statistic is derived from Cochran's Q, a chi-squared (χ^2) test that assesses whether observed differences in effect sizes are due to chance. It estimates the proportion (as a percentage) of total variability across studies that can be attributed to heterogeneity rather than sampling error. The formula for calculating the percentage of heterogeneity of meta-analytical studies is $I^2 = [(Q - df) / Q] \times 100\%$, where Q is the chi-squared statistic and df represents its degrees of freedom (Higgins & Green, 2009). Where possible, subgroups analyses were performed to explain statistical heterogeneity. Sensitivity analysis was also performed to confirm that the meta-analytic results were not influenced by questionable decisions. This involved re-performing the overall effect meta-analysis while excluding studies that appear to adhere more arbitrary or unclear criteria, aiming to ensure the robustness of the findings (Higgins & Green, 2009).

The planned stratified analyses compared groups based on:

- Definitions of multimorbidity: co-occurrence of two or more chronic conditions (MM2+); co-occurrence of three or more chronic conditions (MM3+).
- Whether the total number of included chronic conditions in multimorbidity measurement did or did not exceed the 12 morbidities (a widely accepted threshold (Fortin et al. 2012).

- Sex differences in multimorbidity risk
- Participant sampling age (≤ or > 45yrs)
- Mortality rate derived from the co-existence of multimorbidity and SNAP multibehaviours.

These analyses were chosen given their importance in multimorbidity literature. Furthermore, to avoid possible double counting when examining the overall pooled effect of SNAP multibehaviours on multimorbidity risk (mainly due to the existence of multiple exposure groups within individual studies), only one pair of exposures per study was selected (the one with the smallest magnitude effect) and the rest were excluded. For example, if a study examined the effect of two, three and four SNAP multibehaviours on multimorbidity risk, then only the pair of SNAP health behaviours (the most conservative estimation) was included in the meta-analyses of the overall pooled effect.

Relative effect measures of odds ratios (OR) and hazard ratios (HR) were chosen for the present study using transformations where outcomes were examined differently. Finally, GRADE methodology was used to evaluate the strength of evidence of the most important outcomes. This allows an outcome-based (rather study-based) evaluation of meta-analytic evidence that goes beyond risk of bias examination, providing further confidence in the pooled outcome (Guyatt et al. 2011).

3.3 Results

3.3.1 Studies included

After the exclusion of duplicates, the search strategy yielded 15,633 articles for titles and abstract screening, which identified 55 studies for full-text examination (Figure 2). Thirty-nine studies were excluded (29 examined the association of individual health risk behaviour with multimorbidity; 1 examined the association of health risk behaviours with interim health related risk factors (e.g., high blood pressure) but not morbidities; 3 examined the combined effect of health risk behaviours with mortality risk without any multimorbidity interference; 2 examined solely the clustering of health risk behaviours; 2 examined the combined effect of health risk behaviour to single morbidity; 1 examined an intervention effect on health-related behaviours but not in multimorbidity; 1 examined the association between multibehaviours and mental health comorbidities).

Following two more articles identified via the references they were also included to the final list which in total, were 18 studies under investigation (Adams et al. 2017; Agrawal et al. 2016; Balto et al. 2017; Barreto & Carvalho, 2009; Dhalwani et al. 2017; Fortin et al. 2014; Katikireddi et al. 2017; Linardakis et al. 2015; Loprinzi, 2015; Singh-Manoux et al. 2018; Shao et al. 2021; Shang et al. 2020; de Almeida et al. 2020; Chudasama et al. 2020; Freisling et al. 2020; Kim et al. 2013; Hawks et al. 2011; Halvala et al. 2014).

3.3.2 Study design

Details of the included studies are provided in Table 2. Briefly, most (*n*=11) studies applied a cross-sectional design (Adams et al. 2017; Agrawal et al. 2016; Balto et al. 2017; Barreto & Carvalho, 2019; Fortin et al. 2014; Katikireddi et al. 2017; Linardakis et al. 2015; Loprinzi, 2015; Shao et. al. 2020; de Almeida et al. 2020; Kim et al. 2013) and seven adopted a cohort design (Dhalwani et al. 2017; Singh-Manoux et al. 2018; Hawkes et al. 2011; Shang et al. 2013; Freisling et al. 2020; Chudasama et al. 2020 Halava et al. 2014). All but one study (Balto et al., 2017) used data from existing large datasets derived from general populations, totalling 1,355,041 participants. All studies were published from 2009 onwards.

3.3.3 Country of study

Most studies (*n*=14) were conducted in high-income countries: three in USA (Adams et al. 2017; Balto et al. 2017; Loprinzi, 2015), five in the UK (Dhalwani et al. 2017; Katikireddi et al. 2017; Singh-Manoux et al. 2018; Kim et al. 2013; Chudasam et al. 2020), one in Canada (Fortin et al. 2014), two in Australia (Hawkes et al. 2011; Shang et al., 2020) one in Finland (Halava et al. 2014) and two in EU countries (Linardakis et al. 2015; Freisling et al. 2020). Four studies were implemented in middle income countries: two in Brazil (Barreto & Carvalho, 2019; de Almeida et al. 2020), one in India (Agrawal et al. 2016) and one in China (Shao et al. 2021).

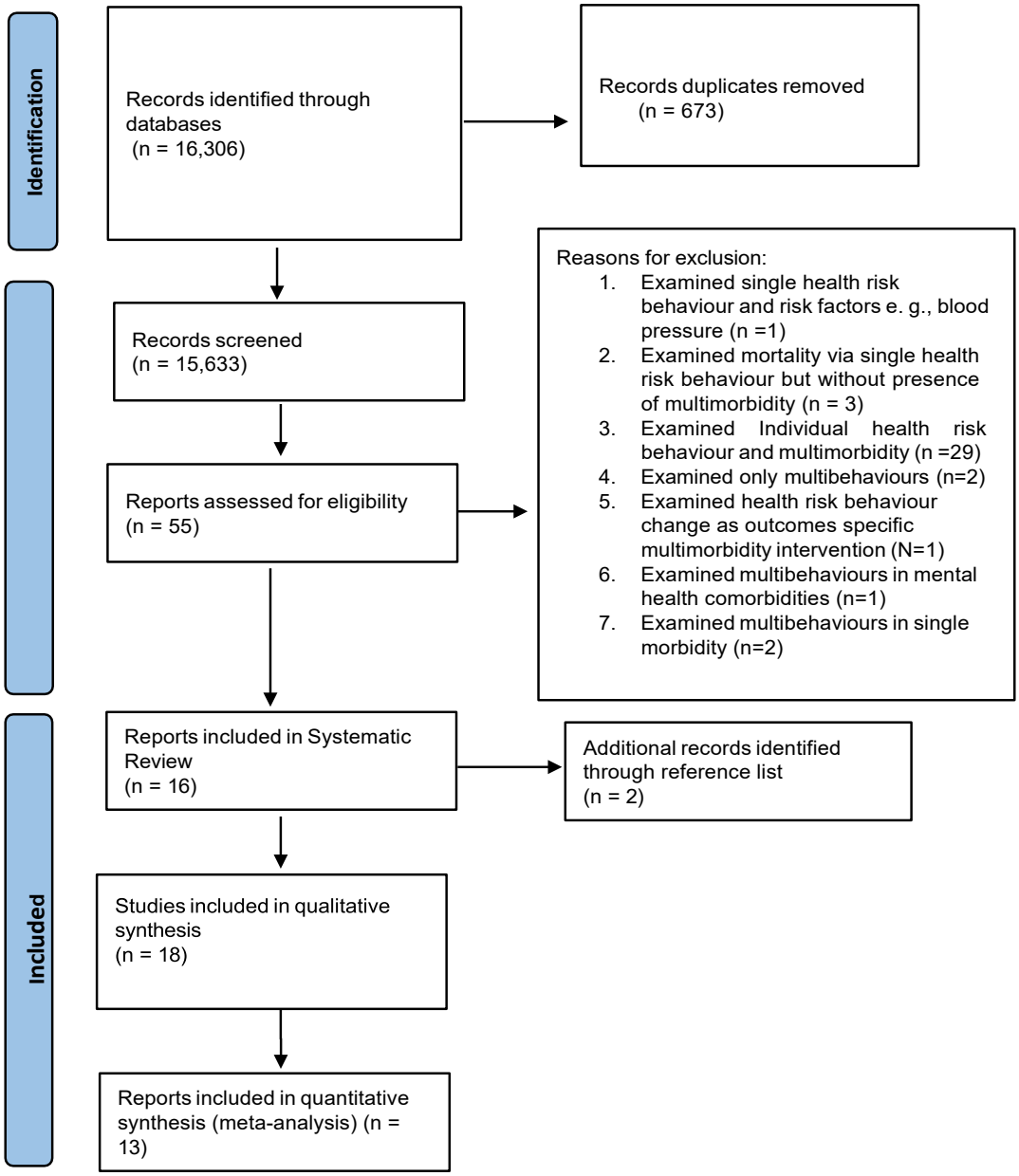

Figure 2. Flow diagram of literature search and screening process

3.3.4 Multimorbidity definition

Fourteen studies directly examined multimorbidity. Nine of those defined multimorbidity as having two or more (MM2+) chronic conditions (Adams et al. 2017; Agrawal et al. 2016; Barreto & Carvalho, 2009; Dhalwani et al. 2017; Loprinzi, 2015; Singh-Manoux et al. 2018; de Almeida et al. 2020; Chudasama et al. 2020, Freisling et al. 2020), one study defined it as having three or more (MM3+) morbidities (Fortin et al. 2014), while two studies applied multiple definitions (MM2+, MM3+, MM4+) (Katikireddi et al. 2017; Shao et al. 2021). Linardakis et al. (2015) developed their own

measurement to investigate the multiple health status of each participant. The remaining four studies examined various comorbidities (Balto et al. 2017; Kim et al. 2013; Hawkes et al. 2011; Halava et al. 2014).

Only six studies applied the widely accepted threshold of including twelve chronic conditions (≥12CC) within their multimorbidity measurement (Dhalwani et al. 2017; Fortin et al. 2014; Katikireddi et al. 2017; Loprinzi, 2015; Chudasama et al. 2020; de Almeida et al 2020). The rest used fewer than 12 morbidities (Agrawal et al., 2016; Balto et al. 2017; Barreto & Carvalho; Singh-Manoux et al. 2018; Shao et al. 2021; Linardakis et al. 2015; Shang et al. 2020; Freiling et al. 2020; Hawkes et al. 2011; Kim et al 2013; Halava et al.,2014). One study examined outcomes both below and above the 12CC threshold (Adams et al. 2017).

3.3.5 Multibehaviours measurement

Ten studies examined all four SNAP health behaviours under investigation (Adams et al. 2017; Agrawal et al. 2016; Dhalwani et al. 2017; Fortin et al 2014; Singh-Manoux et al., 2018). Seven studies investigated various combinations of three of SNAP health behaviours (Barreto & Carvalho, 2009; Linardakis et al. 2015; Loprinzi, 2015), while one study examined a specific combination of only two (Balto et al. 2017).

All but four studies (de Almeida et al. 2020 Balto et al. 2017; Kim et al. 2013; Halava et al. 2014) (*n*=14) presented multimorbidity risk factors that were not considered in present review, such as obesity and sleep (i.e., not SNAP)). Table 3 presents all the lifestyle risk factors examined from each one of the included studies. The most commonly reported non-health risk behaviour factor was obesity.

3.3.6 Measures of multimorbidity-multibehaviours association

Four studies investigated the health-enhancing effect of the SNAP health behaviours in multimorbidity (i.e., not smoking, being physically active) (Loprinzi, 2015; Chudasama et al. 2020; Shang et al. 2020; Freinling et al. 2020). Therefore, the reciprocal (1/x) equation was applied to match the rest of the studies (Higgins & Green, 2009).

Data extraction depended on the reported overall composite measure(s) of exposure of "any" of two or more SNAP health behaviours vs. zero or one health risk behaviour. However, summary data regarding the comparison groups could not be obtained from any of the included studies. For that reason, meta-analytic evidence was based on the reported effect estimates of individual studies, such as OR and HR, using the generic invariance method.

Meta-analyses were based on outcomes derived from the investigation of "any" two, three, or four SNAP health behaviours. For example, Baretto and Carvalho (2009) presented only a single composite outcome measure that included more health risk factors than the four SNAP health risk behaviours considered in this review, and was therefore excluded from all meta-analytic comparisons. This was the only study to provide evidence that contradicted the outcomes of all other studies in this review by indicating an inverse association between multibehaviours exposure and multimorbidity risk for both men and women.

Finally, twelve studies reported their outcomes effects as odds ratios (Adams et al. 2017; Agrawal et al. 2016; Forting et al. 2014; Katikereddi et al. 2017; Linardakis et al. 2015; Loprinzi, 2015; Baretto & Carvalho, 2009; Shao et al. 2021; de Almeida et al. 2020; Kim et al. 2013; Hawkes et al. 2011; Halava et al. 2014); five studies reported hazard ratios (Shang et al. 2020, Dhalwani et al. 2016; Singh-Manoux et al. 2018; Chudasama et al. 2020; Freisling et al. 2020), and one study reported a Cliff's delta (*d*) (Balto et al. 2017). Hazard ratios were treated as a snapshot risk and treated similar to relative risk (RR) according to recommendations of the Cochrane group (Higgins & Green, 2009). Cliff's *d* transformation to odds ratio was based on the guidance from Cliff and Norman (1993).

Table 2. Characteristics of included studies

Study / Country	Settings	Race Ethnicity	Main objective	Age	Sample size	Cut off MM	Number of Diseases	Risk Factors	Health Risk Behaviours of interest	Outcome measure	Main findings
Adams, et al. 2017 USA	General population from 50 US states	non-Hispanic white, Black or African American, Hispanic of any race, American Indian/Alaska Native, and other	To test the hypothesis if there is a linear association between the number of RF's and MCC rates	≥18 yrs.	Behavioural Risk Factor Surveillance System (BRFSS) data n=400,411	2+CC	MCC8 n=8 CC & MCC12 n=12CC (asthma, arthritis, chronic obstructive pulmonary disease, cognitive impairment heart disease, stroke, cancer other than skin, chronic kidney disease) plus (depression, hypertension, high cholesterol, and diabetes)	n=5 Smoking, inadequate fruit/vegetables consumption, sedentary lifestyle, BMI>30, Hours of sleep	n=3 Smoking, Inadequate fruit/vegetables consumption, sedentary lifestyle	(ORs) 95% CI	For all combinations of MCCs and composite RF measures each additional RF significantly increased the percentage of adults reporting MCC
Agrawal et al. 2016 INDIA	General population from six selected states in India (Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh, and West Bengal)	Indian	To test the hypothesis that the accumulation of unhealthy lifestyle factors increases the likelihood of reporting	≥18 yrs.	(WHO SAGE) survey, wave1 which conducted in India in 2007 n=12,198 (4,747 males, 7,481females)	2+CC	n=9 CC (angina, arthritis, asthma, cataract, depression, diabetes, hypertension, chronic lung disease, and stroke)	n=5 Tobacco use, Alcohol use, Insufficient fruit/vegetables consumption, Physical inactivity, BMI	n=4 Tobacco use, Alcohol use, Insufficient fruit/vegetables consumption, Physical inactivity	(ORs) 95% CIs .	The accumulation of multiple unhealthy lifestyle factors progressively increased the likelihood of multiple NCDs.
		English		≥50 yrs.		2+CC					

Singh-Manoux et al. 2018 ENGLAND	London based office staff, aged 35–55 (at baseline), working in 20 civil service departments		To examine how socioeconomic, behavioural, and clinical risk factors shape the development, progression, and outcome of cardiometabolic multimorbidity.		Whitehall cohort with mean follow-up of 23.7 years (1985 to 2017) n= 8,270 (6,895 men and 3,413 women)		n=4 cardiometabolic multimorbidity (at least 2 of diabetes, coronary heart disease, and stroke),	Three set of RF (a) clinical profile (hypertension, hypercholesterolemia, overweight/ obesity, family history of cardiometabolic disease), (b) sociodemographic (occupational position), (c) behavioural factors (smoking, alcohol consumption, diet, physical activity).	n=4 Smoking, Alcohol Diet, Physical activity	(HRs) 95% CIs	Behavioural factors (physical activity, alcohol consumption, diet, and smoking) determined progression to multimorbidity among participants with cardiometabolic disease
Balto et al. 2017 USA	online National MS Society Local Research page	US Caucasian	To examine that the co-occurrence of poor diet and insufficient levels of physical activity would synergistically impact comorbidities and underperformance outcomes in people with MS	18- 64 yrs.	69 persons with MS.	2+CM	n=3 (high cholesterol, diabetes, cancer)	n=2 physical inactivity, insufficient consumption of fruits/vegetables	n=2 physical inactivity, insufficient consumption of fruits/vegetables	(ORs) 95% CIs	the cluster of co-occurring poor diet and insufficient physical activity is synergistically associated with comorbidities in persons with MS
Dhalwani et al. 2016 ENGLAND	English Longitudinal Study of Ageing (ELSA)	English	To model the incident rates of MM with adjusted hazard ration (aHR) and associated with five individual lifestyle factors first	≥50 yrs.	N=5476	2+CC	n=19 (diabetes, hypertension, stroke, myocardial infarction, congestive heart failure, angina, lung disease, chronic obstructive pulmonary disease, asthma, arthritis, osteoporosis, cancer, hearing problems, Parkinson's, Alzheimer's, dementia, macular degeneration, and glaucoma)	n=5 Smoking, Alcohol, fruit/vegetables Physical inactivity, BMI	n=4 Smoking, Alcohol, fruit/vegetables Physical inactivity,	(HRs) 95% CIs	Compared with having no risk factors, having 2, 3, and 4 or more unhealthy lifestyle factors was associated with a greater multimorbidity hazard

Fortin et al. 2014 CANADA	General population from four local healthcare networks in Quebec, Canada.	Canadian	To test the hypothesis that the accumulation of unhealthy lifestyle factors is associated with increased likelihood of multimorbidity	≥45 yrs.	(Program of Research on the Evolution-of a Cohort Investigating Health System Effects, PRECISE) [n=1,196 (Men n = 515, Women n = 681)	3+CC	n=14 (hypertension, cholesterol elevated, asthma, chronic obstructive pulmonary disease, diabetes, thyroid disorder, osteoarthritis, rheumatoid arthritis, osteoporosis, colon problem, angina/coronary artery disease, stroke, congestive heart failure, and cancer)	n=5 Smoking, Alcohol, fruit/vegetables Physical inactivity, BMI	n=4 Smoking, Alcohol, fruit/vegetables Physical inactivity,	(ORs) 95% CIs	When lifestyle factors were combined, starting from a threshold of 2 lifestyle factors in women and 4–5 in men, accumulating unhealthy lifestyle factors progressively increased the likelihood of multimorbidity
Katikireddi et al., 2017 SCOTLAND	General population of 62 sampling units/postcode sectors, from the Central Clyde side conurbation (including Glasgow city) of west Scotland	Scottish plus a sample of 30-to 40 yrs. old South Asians	To describe the development and social patterning of multimorbidity over the life course and quantify the contribution of behaviour-related risk factors.	Three cohorts of 35,55,75 yrs. old	Twenty -07 study –W4 (2007-2008 n=2604)	2+CC/3+ CC 2+CC	n=40 CC Hypertension, Depression, Painful condition, Asthma (currently treated), Coronary heart disease, treated dyspepsia, Diabetes, Thyroid disorders, Rheumatoid arthritis, Hearing loss, Chronic obstructive pulmonary disease, Anxiety, Irritable bowel syndrome, cancer in last five years, Alcohol problems, psychoactive substance misuse, Treated constipation, stroke, Chronic kidney disease, Diverticular disease of intestine, Atrial fibrillation, Peripheral vascular disease, Heart failure, Prostate disorders, Glaucoma, Epilepsy, Dementia, Schizophrenia, Psoriasis, Inflammatory bowel disease, Migraine, Blindness & low vision, Chronic sinusitis, Learning disability, Anorexia or bulimia, Bronchiectasis, Parkinson's disease, Multiple sclerosis, Viral Hepatitis, Chronic liver disease	n=5 Smoking, Alcohol, fruit/vegetables Physical inactivity, BMI	n=4 Smoking, Alcohol, fruit/vegetables Physical inactivity	(ORs) 95% CIs	Risk factors count were stronger predictors of multimorbidity when it was defined as being three or more conditions rather than two 2RF

Linardakis et al. 2015 EU	SHARE (Survey of Health, Ageing, and Retirement in Europe) in 11 European countries (Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, and Switzerland).	European citizens	To assess the presence of multiple BRFs in adults aged 50 years or older in 11 European countries, according to their physical and mental health status.	≥50 yrs.	SHARE (Survey of Health, Ageing, and Retirement in Europe) n=26,026	2+CC, symptoms, (I) ADL	**11 Chronic conditions** (heart attack, high blood pressure, high blood cholesterol, stroke, diabetes or high blood glucose, chronic lung disease, asthma, arthritis, osteoporosis, cancer, and stomach or duodenal/ peptic ulcer) **11 symptoms** (pain in back, knees, hips or other joints; heart trouble; breathlessness; persistent cough; swollen legs; sleeping problems; falls; fear of falling; dizziness, faints, or blackouts; stomach or intestine problems; and incontinence) **13 activities** (dressing (including shoes and socks), walking across a room, bathing or showering, eating or cutting up food, getting in or out of bed, using the toilet using a map in a strange place, preparing a hot meal, shopping for groceries, making telephone calls, taking medications, doing work around the house or garden, or an aging money)	n=4 Tobacco use, Alcohol use, physical inactivity, BMI	n=3 Tobacco use, Alcohol use, physical inactivity	(ORs) 95% CIs	The findings indicate a positive relationship between the presence of 2 or more BRFs and physical and mental health status components; , displaying higher presence and clustering of these components
Loprinzi, 2015 USA	General population National Health and Nutrition Examination Survey (NHANES) US	Mexican American, non-Hispanic white, Non-Hispanic black, other US citizens	To examine the extent to which multibehaviours are associated with multimorbidity	≥20 yrs.	General population National Health and Nutrition Examination Survey (NHANES) n=2048	2+CC	n=14 arthritis, asthma, bronchitis,- cancer, congestive heart failure, coronary artery disease, diabetes, emphysema, liver disease, stroke, overweight or obese, high total cholesterol level, low high-density lipoprotein cholesterol (HDL-C) level, and hypertension	n=4 Health enhancing behaviours (active, healthy diet, no smoker, and adequate sleep)	n=3 (active, healthy diet, no smoker)	(ORs) 95% CIs	Dose-response association was observed in that participants who engaged in more health-enhancing behaviours were less likely to be multimorbid,

Barreto & Carvalho, 2009 BRAZIL	General population from 26 Brazilian capitals and Federal District	Brazilian	To assess the association between chronic diseases and health risk behaviours … by sex	≥30 yrs.	VIGITEL sample n=39,821 adults, (24,788 women)	2+CC	n=4 diabetes, hypertension, myocardial infarction and/or stroke	n=6 Consumption of red meat or poultry with skin, consumption of whole milk, consumption of frit/vegetables, physical inactivity, smoking)	n=3 consumption of frit/vegetables, physical inactivity, smoking)	(ORs) 95% CIs	Number of risk behaviours were inversely associated with reporting two or more NCD in both men and women.
Shao et al. 2021 CHINA	China Health and Retirement Longitudinal Study (CHARLS), which covers 450 communities in 150 counties, 28 provinces in mainland China	Chinese	To investigate the associations of the five individual lifestyle factors (sleep duration, physical activity, smoking, drinking, and body weight status) and their accumulating effects with the occurrence of multimorbidity in Chinese community dwellers	≥45 yrs.	N=6,951	2+CC/3+ CC/4+C C	n=11 (i) hypertension; (ii) dyslipidaemia; (iii) diabetes or high blood sugar; (iv) cancer or malignant tumour; (v) chronic lung diseases; (vi) liver disease (except for fatty liver, and cancer); (vii) heart attack, coronary heart disease, or other heart problems; (viii) stroke; (ix) kidney disease (except for cancer); (x) stomach or other digestive disorders (except for cancer); (xi) emotional, nervous, or psychiatric problems; (xii) memory-related disease; (xiii) arthritis or rheumatism; and (xiv) asthma	n=5 sleep duration, physical activity, smoking, drinking, and body weight status)	n=3 physical activity, smoking, drinking,	(ORs) 95% CIs	The results indicated that the number of high-risk lifestyle factors increased the risk of multimorbidity, and the influence became more significant when the number of diseases increased

Shang et al. 2020 AUSTRALIA	Sax Institute's 45 and Up Study in New South Wales (NSW), Australia	Australian	To evaluate the importance of lifestyle factors on the development of multimorbidity and analysing the association of selected modifiable health factors with incident multimorbidity	≥45 yrs.	N=53,867	2+CC/3+CC/4+CC	n=11 (non-melanoma skin cancer), heart disease, stroke, hypertension, dyslipidaemia, diabetes, asthma, mental disorders (depression and anxiety),degenerative disorders (dementia and Parkinson's disease), hip replacement, and osteoarthritis	n=6 dietary intake, smoking, alcohol consumption, physical activity, sleep and sitting time	n=4 nutrition smoking, alcohol physical activity	(HRs) 95% CIs	Modifications on behavioural factors including diets, physical activity, smoking, alcohol consumption may reduce the risk of multimorbidity in middle-aged adults, whereas individuals with low socioeconomic status or psychological distress are at the highest priority for intervention
de Almeida et al. 2020 BRAZIL	Brazilian Longitudinal Study of Aging (ELSI-Brazil)	Brazilian	To evaluate associations between unhealthy lifestyle factors (individual and combined) and multimorbidity among Brazilian men and women aged 50 years and older.	≥50 yrs.	N=7,918	2+CC	n=26 (cataract, glaucoma, diabetic retinopathy, macular degeneration, hypertension, diabetes, high cholesterol, heart problems (infarction, angina and heart failure), stroke, asthma, lung diseases (emphysema, chronic bronchitis or chronic obstructive pulmonary disease), arthritis or rheumatism, osteoporosis, spinal disorder, cancer, chronic renal failure, depression, Parkinson's and Alzheimer's disease)	n=4 fruit/vegetables, smoking, alcohol physical activity	n=4 fruit/vegetables, smoking, alcohol physical activity	(ORs) 95% CIs	
Chudasama et al. 2020 UK	UK Biobank from 22 sites across England, Wales, and Scotland		whether and to what extent a healthy lifestyle impacts on longevity in people with multimorbidity	≥38 yrs.	N= 480,940	2+CC	n=36	n=4 leisure-time physical activity, smoking, diet, and alcohol consumption	n=4 leisure-time physical activity, smoking, diet, and alcohol consumption	(HRs) 95% Cis	

Freisling et al. 2020 EU	EPIC-InterAct study on seven out of ten participating European countries	European citizens	To investigate associations between five lifestyle factors and incident multimorbidity of cancer and cardiometabolic diseases	43-58 yrs.	N= 291,778	2+CC	n=3 cancer, CVD, T2D	n=5 Smoking, Alcohol, Mediterranean diet, Physical inactivity, BMI	n=4 Smoking, Alcohol, Mediterranean diet, Physical inactivity	(HRs) 95% CIs	A higher HLI, reflecting healthy lifestyles, was strongly inversely associated with multimorbidity
Kim et al. 2013 UK	British Women's Heart and Health Study	British Women	To evaluate the 'overall health benefit' attributable to the lifestyles of older women	60-79 yrs.	N= 4,286	2+CM	n=2 arthritis and locomotor disability, CVD	n=2 arthritis and locomotor disability, CVD	n=4 smoking, alcohol intake, fruit/vegetables, physical activity	(ORs) 95% CIs	Low Population attributable factors suggest changes in health-related behaviours in older women would result in only modest reductions in common chronic conditions.
Hawkes et al. 2011 AUSTRALIA	Colorectal Cancer and Quality of Life Study,	Australian	To assess self-reported lifetime prevalence of cardiovascular disease (CVD) among colorectal cancer survivors, and examine the cross-sectional and prospective associations of lifestyle factors with co-morbid CVD.	20-80 yrs.	N= 1,966	2+CM	n= 7 (colorectal cancer, six CVD categories (hypercholesterolaemia, hypertension, diabetes, heart failure, kidney disease, and ischaemic heart disease (IHD))	n=5 body mass index, physical activity, television (TV) viewing, alcohol consumption, and smoking.	n=3 physical activity, alcohol consumption, and smoking.	(ORs) 95% CIs	Overweight colorectal cancer survivors were more likely to suffer from co-morbid CVD.
Halava et al. 2014 FINLAND	Finnish Public Sector Study/ 10 municipalities & 21 hospitals	Finnish	To investigate the association between lifestyle factors and nonadherence to statin therapy among patients with and without cardiovascular comorbidities	24-75 yrs.	N= 9,285	2+CM	CVD + comorbidities'	n=4 Smoking, Alcohol, Physical inactivity, BMI	n=3 Smoking, alcohol intake, physical activity	(ORs) 95% CIs	cluster of 3–4 lifestyle risks predicted increased odds of nonadherence after adjustment for sex, age and year of statin initiation

2+CC= Two or more chronic conditions; 3+CC= Three or more chronic conditions; 2+CM= Two or more comorbidities; MCC= Multiple chronic conditions; MCC8 = Multiple chronic conditions with eight morbidities; MCC12= Multiple chronic conditions with twelve morbidities; NCD-=non-communicable diseases; ADL=Activities of daily living; RF= Risk factor; MM= Multimorbidity; MS=Multiple sclerosis; OR= Odds ratio; HR= Hazzard ratio

Table 3. Examining risk factors and health risk behaviours of included studies

Study	Health Risk Behaviours						Other lifestyle-related risk factors				
	Smoking	Diet (5 F/V a day)	Alcohol	Physical (in) activity	Sleep	Other	Obesity	Diabetes	Hypertension	Hypercholesterolemia	Other
Adams et al. 2017	x	x		x	x		x	x	x	x	x
Agrawal et al. 2016	x	x	x	x			x				
Singh-Manoux et al.2018	x	x	x	x			x		x		x **
Balto et al. 2017		x		x							
Dhalwani et al. 2016	x	x	x	x			x				
Fortin et al. 2014	x	x	x	x			x				
Katikireddi et al. 2017	x	x	x	x			x				
Linardakis et al. 2015	x		x	x			x				
Loprinzi, 2015	x	x		x	x						
Barreto & Carvalho, 2009	x	x		x		x*					
Shao et al. 2021	x		x	x	x		x				
Shang et al. 2020	x	x	x	x	x	x***					
de Almeida et al. 2020	x	x	x	x							
Chudasama et al. 2020	x	x	x	x							
Freisling et al. 2020	x	x	x	x			x				
Kim et al. 2013	x	x	x	x							
Hawkes et al. 2011	x		x	x							
Halava et al. 2014	x		x	x			x				

* Consumption of red meat or poultry with skin, consumption of whole milk)

**Cardiometabolic disease

*** Sitting time

3.3.7 Risk of bias

All studies, except one (Balto et al. 2017) adjusted their results for the most known important confounders such as age, sex, socio-economic indicators (education, income, poverty, area of living, marital status, and race/ethnicity). Risk of bias was considered moderate for 16 studies and high for two (Barreto & Carvalho, 2009; Balto et al. 2017), mainly due to inadequate controlling for potential confounders (Figure 3 and Figure 4). Specifically, the Balto et al. (2017) study had a limited number of participants, used a convenience sampling methodology, and did not adjust for potential confounders in analysis. Barreto and Carvalho (2009) acknowledged that the finding of inverse association between multibehaviours and multimorbidity was a product of reverse causality. This was attributed to either spectrum bias in relation to the limited number of morbidities included in multimorbidity measurement, or misclassification bias (specifically response and recall biases as a result of self-reported data collection).

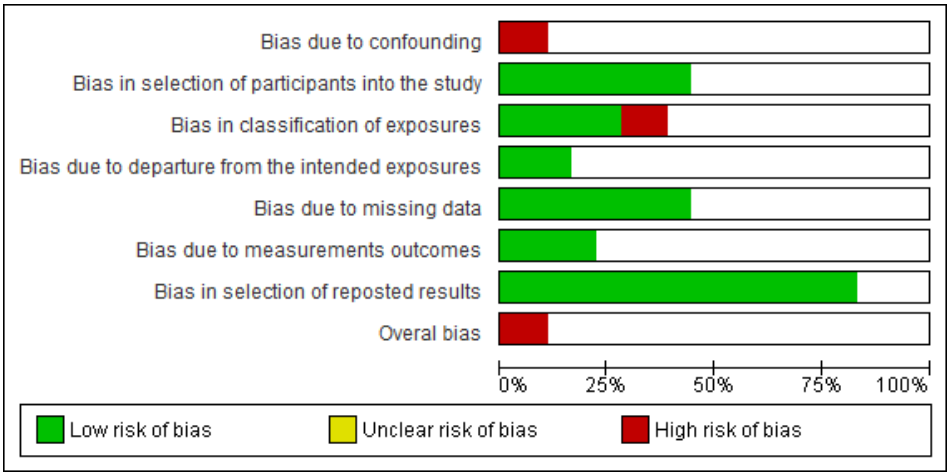

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias domain presented as percentages across all included studies

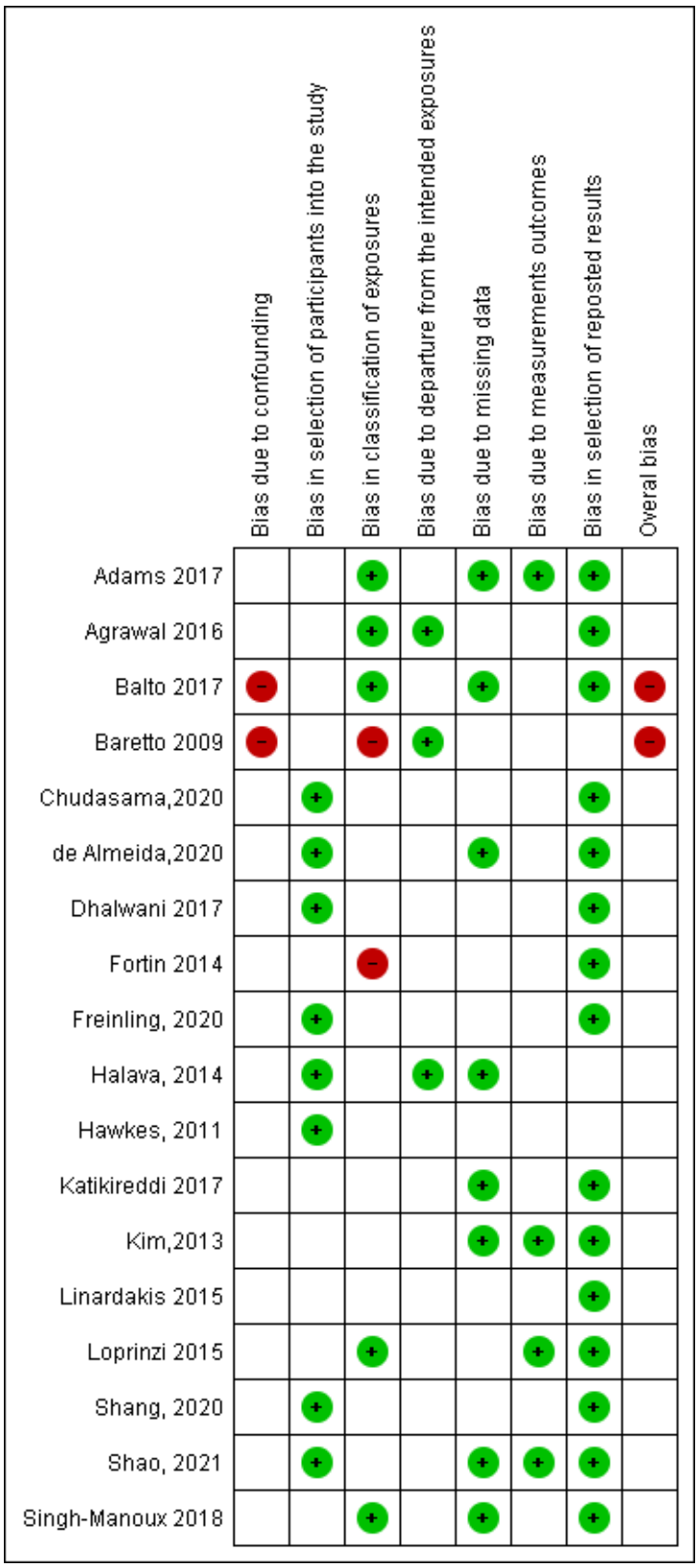

Figure 4. Risk of bias summary: Authors' judgements about each risk of bias item for each included study

3.3.8 Association between SNAP exposures and primary outcome, multimorbidity risk

3.3.8.1 Overall analysis of the association between SNAP exposures and multimorbidity risk

A conservative estimate derived from seven studies (Adams et al. 2017; Agrawal et al. 2016; Balto et al. 2017; Fortin et al. 2014; Katikireddi et al. 2017; Linardakis et al. 2015; Loprinzi, 2015), of *n*=459,352 showed an increase odds of 65% for developing multimorbidity, in comparison with those having no engagement at all or at least with one health risk behaviour [(OR=1.65 95% CI: 1.38, 1.97; I^2=81%); Grade moderate: (-1 level: inconsistency; -1 indirectness)] (Appendix 4 – Table A4.1). Sensitivity analysis that excluded two studies (Balto et al., 2017; Linardakis et al., 2015) had little impact on the pooled effect (OR = 1.62 95% CI: 1.31, 2.00 I^2=86%) (Appendix 4 - Table A4.2).

Subgroup analyses to explain the accompanied considerable heterogeneity (I^2=81%) suggested that the effect was neither moderated by type of multimorbidity definition (Chi^2=0.77, df=1, p=0.38) I^2=0%), nor sampling age (Chi^2=1.57, df=1, p<.21 I^2=36.2%), since no differences were found between specific subgroups (Appendix 4 - Table A4.3 and Table A4.4). However, subgroup analyses on the number of morbidities used to define multimorbidity showed that the overall pooled effect of those studies who examined fewer than 12 morbidities was significantly greater (OR=2.01 95%CI: 1.85, 2.19 I^2=0%) than those which explored a number of morbidities above the proposed limit (OR=1.40 (95%CI 1.16, 1.70; I^2=60%), with difference between subgroups (Chi^2=11.74, df=1, p<.0006) I^2=91.5%. (Appendix 4 – Table A4.5).

For any two SNAP behaviours, the four studies (*n*=419,560) that examined fewer than 12 morbidities (<12CC) showed an 88% increased odds of multimorbidity [(OR=1.88 95% CI:1.72, 2.05 I^2=0%) Grade high: (-1 inconsistency, -1 indirectness, +1 imprecision + dose responses)] (Appendix 4 - Table A4.6). By comparison, the pooled estimate across the four studies (*n*=414,177) that examined 12 or more morbidities (≥12CC) showed a weaker, but still significant increase in odds [(OR=1.53 95%CI: 1.17, 2.01 I^2=89%) Grade moderate: (-1 inconsistency, -1 indirectness, +1 imprecision + dose responses)] (Appendix 4 – Table A4.7). This difference was reversed when exploring the effect of three SNAP risk behaviours. The pooled effect was higher for both subgroups, but for those studies using ≥12CC, the odds of multimorbidity increased to two and a half times (OR=2.52 95% CI:1.99, 3.20 I^2=66%) (Appendix 4 – Table A4.8), whereas for <12CC

studies, the odds were doubled (OR=2.02 95% CI:1.55, 3.55 I^2=97%) (Appendix 4 – Table A4.9). All four SNAP health risk behaviours were examined in two studies (*n*=3,800) and only for ≥12CC where, as expected, the odds of multimorbidity were even higher (OR=2.72 95% CI:1.52, 4.85 I^2=60%) (Appendix 4 – Table A4.10).

3.3.8.2 Stratified analysis by numbers of SNAP multibehaviours

Analyses of the effect of health risk behaviours showed a positive dose response association between the number of SNAP behaviours and multimorbidity risk. Moreover, the association was stronger when the same number of SNAP multibehaviours examined multimorbidity definitions with higher cut-off points. For any two, three or four SNAP health risk behaviours, the pooled effect outcome indicated a stronger positive association for MM3+ definition than for MM2+.

Specifically, the pooled effect of two SNAP multibehaviours, examined by three studies (*n*=10,751) doubled the odds for MM3+ (OR=2.04 95%CI: 1.66, 2.50 I^2=0%), while it was only increased by 69% (OR=1.58 95%CI: 1.26, 1.99 I^2=90%) for MM2+, as six studies examined (*n*=432,130) (Appendix 4 – Table A4.11 and A4.12). Similarly, when three SNAP multibehaviours were examined, the pooled effect for MM2+ was double (OR=1.96 95%CI: 1.31, 2.96 I^2=96%); while for MM3+ was more than tripled (OR=3.15 95%CI: 2.46,4.03 I^2=0%) (Appendix 4 – Table A4.13 and A4.14). As for engaging with all four SNAP multibehaviours, the odds were doubled (OR=1.98 95%CI:1.64, 2.39 I^2=32%) for the MM2+ definition, as shown by two studies (*n*=14,802), and tripled (OR=3.04 95%CI:2.26, 4.08 I^2=0%) with MM3+, as found in two studies (*n*=3,800) (Appendix 4 – Table A4.15 and A4.16).

As expected, the pattern was replicated by the only study that examined the combined effect of SNAP health risk behaviours on multimorbidity using the MM4+ definition (Shao et al., 2021). This showed that for two SNAP health risk behaviours, the odds were double with four or more co-occurring morbidities (OR=2.3 95% CI: 1.5,03.6 p<.05), while it was more than tripled when three SNAP health behaviours were examined (OR=3.5 95% CI:2.3 5.5 p<.05).

Finally, the same pattern of pooled effects was also observed in the meta-analysis of four cohort studies (*n*=359,39) that examined the temporal association between SNAP

multibehaviours and multimorbidity. Specifically, the pooled risk of developing multimorbidity in the next 10+ years in those with two or more heath risk behaviours, was 26% higher (HR=1.26 95%CI: 1.18, 1.34 I^2=54%; Grade high) (Appendix 4 – Table A4.17) than in those with zero or one health risk behaviour.

When engagement with specific numbers of SNAP health risk behaviours was examined, their incremental influence became clearer. The risk of acquiring multimorbidity was doubled in relation to engagement in all four SNAP multibehaviours (HR=2.00 95%CI:1.19, 3.37 I^2=82%) (Appendix 4 – Table A4.18), decreasing by 37% for three multibehaviours (HR=1.63 95%CI:1.10, 2.43 I^2=0%) (Appendix 4 – Table A4.19) and 51% for two (HR=1.49 95%CI:1.27, 1.76 I^2=0%) (Appendix 4 – Table A4.20).

Mortality rates in the presence of multimorbidity and SNAP multibehaviours were examined by two studies (*n*=489,210). Mortality risk was more than double when someone with multimorbidity engaged in all four SNAP behaviours [(HR=2.63 95% CI: 2.09, 3.29 I^2=79%) Grade high: (+1 inconsistency, +1 indirectness, +1 imprecision + dose responses)] (Appendix 4 – Table A4.21), decreasing to a doubling of risk with three multibehaviours (HR=2.00 95% CI: 1.71, 2.34 I^2=69%) (Appendix 4 – Table A4.22) and a 45% increase in risk with two (HR=1.45 95% CI: 1.16, 1.83 I^2=65%) (Appendix 4 – Table A4.23).

3.3.8.3 Stratified analysis by sex differences

Data extraction for sex was only possible for four observational studies (Fortin et al. 2014; Linardakis et al. 2015; Shao et al. 2021; de Almeida et al. 2020) and one cohort study (Chudamasa et al. 2020), totalling (*n*=523,03) participants. The threshold of multibehaviours for developing multimorbidity differed by sex. For men, the threshold was based mostly on number of SNAP health risk behaviours, but for women the threshold was related to multimorbidity definition.

Engagement with two SNAP risk behaviours was not significantly associated with multimorbidity either for MM2+ OR=1.16 95% CI:0.96, 1.41 I^2=0%) (Appendix 1 – Table A4.24) or MM3+ (OR=1.53 95% CI:0.92, 2.53 I^2=0%) for men (Appendix 4 – Table A4.25). In women, the association between engagement with two SNAP behaviours and multimorbidity was marginally non-significant when using the MM+2 definition

(OR=1.54 95% CI: 0.98, 2.41 I^2=86%) (Appendix 4 – Table A4.26); though for MM+3 definition the pooled effect showed a double odds for multimorbidity (OR=2.23 95% CI: 1.70, 2.92 I^2=0%) (Appendix 4 – Table A4.27).

With three SNAP behaviours the odds of developing multimorbidity were significantly increased for both sexes. For men, although the association was marginally significant using the MM+2 definition [(OR=1.45 95% CI: 1.01, 2.10 I^2=45%) Grade low: (-1 inconsistency, -1 indirectness, -1 imprecision + dose responses)] (Appendix 4 – Table A4.28), the odds were tripled when using the MM+3 definition (OR=2.91 95% CI: 1.46, 5.82 I^2=0%) (Appendix 4 – Table A4.29). In women, the association was not statistically significant for MM+2 [(OR=1.59 95% CI: 0.90, 2.80 I^2=85%) Grade low: (-1 inconsistency, -1 indirectness, -1 imprecision + dose responses)] (Appendix 4 – Table A4.30) but the odds of multimorbidity were more than tripled using MM+3 (OR=3.34 95% CI: 2.50, 4.45 I^2=0%) (Appendix 4 – Table A4.31).

Chudasama et al. (2020) examined the gain in life expectancy of someone with multimorbidity when engaged in health-enhancing behaviours. They identified that women had better life expectancy than men in all comparisons, which was related to the number of multibehaviours. Particularly, women with multimorbidity reduced the risk of negative outcomes when they engaged with all four SNAP health enhancing behaviours by 60% (HR=0.40 95% CI:0.34, 0.47) compared with 55% in men (HR=0.45 95% CI:0.40, 051). This effect was attenuated but remained significant with three SNAP health enhancing behaviours with 53% in women (HR=0.47 95% CI:0.40, 0.55) and 43% in men (HR=0.57 95% CI:0.51, 0.64). For engagement with two health-enhancing behaviours, the risk of mortality in those with multimorbidity was attenuated beyond significance; reduced to 23% in women (HR=0.67 95% CI:0.49, 0.93), and to 17% in the men (HR=0.83 95% CI: 0.66, 1.03).

3.3.9 Effects of exposures: Secondary outcomes

3.3.9.1 Clustering of SNAP health risk behaviours and Multimorbidity risk

Five studies investigated the health effect of specific clusters of health risk behaviour on multimorbidity or comorbidity risk (Katikireddi et al. 2017; Balto et al. 2017; Dhalwani et al. 2017; Kim et al. 2013; Hawkes et al. 2010). However, no meta-analysis was possible. Three clusters of two SNAP health behaviours were most relevant (physical

activity and healthy diet; physical (in)activity and smoking; and smoking and alcohol drinking). Being physically active and a non-smoker appeared to lower multimorbidity risk [β=-.16 (-0.31, -.01) p=.03] in one epidemiological study (Loprinzi, 2015), while physical inactivity and smoking more than doubled the risk of developing multiple morbidities (AHR=2.35 95%CI: 1.36, 4.08) (Dhalwani et al. 2016). Being physically active and having a healthy diet have also been found to be beneficial for multimorbidity risk, but only in men [β=-.30 (-0.57, -0.04) p=.02] (Loprinzi, 2015). However, regarding the possible comorbidities related with multiple sclerosis, one study indicated that the combination of physical activity and healthy diet could slow down the development of multiple sclerosis (Cliffs d=.33, p=.02) (Balto et al., 2017). Hawkes et al. (2011) examined the development of hypercholesterolaemia, hypertension, IHD and diabetes comorbidities in cancer survivors. Although alcohol consumption and smoking were not significant risk factors, not engaging in any of these behaviours reduced the risk by 77% (OR=0.23 95% CI: 0.07, 0.75). Finally, Kim et al. (2013) suggested that all SNAP health risk behaviours explained only 9% of variance in the incidence of combined conditions (locomotor disability, CVD and arthritis).

3.3.9.2 Multiple health risk behaviours as contributors of multimorbidity social patterning

Only two studies examined the contribution of SNAP health risk behaviours to social patterning of multimorbidity (Katikireddi et al. 2017; Loprinzi, 2015). The authors adjusted the combined effect of SNAP health risk behaviours for other well-known social patterning risk factors, such as area-level deprivation or low income. Results indicated that a combination of all SNAP health risk behaviours had a statistically significant association with social patterning (β=0.05 95% CI: -0.08, -0.02 p=.001) (Loprinzi, 2015), attenuating it by 40.8% (Katikireddi et al. 2017).

3.4 Discussion

3.4.1 Summary of main results

This is the first systematic review and meta-analysis to examine the combined effect of the multimorbidity-multibehaviours association. A central finding was that this association varies depending on the number of SNAP multibehaviours and the operational definition of multimorbidity. For example, the odds of developing multimorbidity, depending on the numbers of involved SNAP multibehaviours, ranged from 65% with two SNAP multibehaviours and MM2+ definition, to over 200% with all four SNAP multibehaviours and MM3+. Furthermore, a positive dose response association was observed between the number of SNAP multibehaviours and multimorbidity risk, that became stronger when the same number of SNAP multibehaviours were examined using multimorbidity defined as three or more, or four or more co-occurring conditions (compared with the more common MM2+ definition). Particularly, with three SNAP multibehaviours the odds were tripled with MM3+ definition whereas they were doubled with MM2+.

Stratified analyses examining sex differences in multimorbidity risk in the presence of SNAP multibehaviours revealed further patterning. In addition to the twofold dose response association, men and women appeared to have a different threshold for developing multimorbidity after their engagement with SNAP multibehaviours. For example, for men, the threshold of significant relationship between multimorbidity and SNAP multibehaviours varied with the number of involved SNAPs (i.e., two or above health risk behaviours), but for women the threshold related exclusively to the applied multimorbidity's operational definition (i.e., MM3+). Specifically, it was found for men the odds of developing multimorbidity using either MM2+ or MM3+ was not significantly affected by their engagement with two SNAP multibehaviours. For women, neither two nor three SNAP multibehaviours were significantly associated with MM2+ multimorbidity.

Studies of mortality rates in the presence of multimorbidity and SNAP multibehaviours provided further support for both emerging patterns. Particularly, the mortality risk that accompany someone's engagement with all four SNAP multibehaviours was more than double, compared with the 46% increased risk of someone's engagement with any two SNAPs. Women were found to have better life expectancy than men when engaging with

the same number of SNAP health-enhancing behaviours (not smoking, being physical active, having a healthy diet and drinking alcohol within the limits).

Finally, though not meta-analytically examined, evidence from two studies showed the importance of the multimorbidity–SNAP multibehaviours associations in relation to health inequalities, whereby SNAP multibehaviours can explain approximately 40% of multimorbidity's social patterning.

However, the considerable heterogeneity among studies from which pooled effects were derived suggests a need for caution when interpretating the magnitude of multimorbidity-SNAP multibehaviours associations. Subgroup analyses identified that a possible source of heterogeneity was methodological mismatch with the proposed threshold of 12CC (as the minimum number of conditions used when assessing multimorbidity prevalence (Fortin et al. 2012)). Multimorbidity studies that involved <12 morbidities produced significantly different association, between multimorbidity and SNAP multibehaviours, compared with those from studies that examined the recommended threshold of ≥12CC or above.

3.4.2 Overall completeness and applicability of evidence/ Agreements and disagreements with other studies or reviews

This review fills a gap in the literature regarding the combined effect of the four most common lifestyle risk factors (smoking, nutrition, alcohol, physical activity) on the development of multimorbidity. In a broader sense, one could argue that the present review answers holistically to the recent call by researchers for more aetiological evidence on common risk lifestyle factors for multimorbidity (Marengoni et al. 2011; Violan et al., 2014). Thus, evidence of the strong dose response association between multimorbidity and SNAP multibehaviours complements and augments evidence from studies that showed significant associations of single SNAP health behaviours with incident multimorbidity (Cao et al. 2019; Jackson et al. 2016; Hussin et al. 2019; Wikstrom et al. 2015), physical decline (Pluijm et al. 2007) and rapidity of multimorbidity progression (Schäfer et al. 2019).

The observed sex pattern supplements our knowledge of known sex differences in the multimorbidity literature (Violan et al. 2014). For example, multimorbidity prevalence

tends to be higher among women than in men, at all ages (Agur et al. 2016; Adad-Diaez et al. 2014; Afshar et al. 2015). The meta-analytic outcomes reported here indicate that the association between multimorbidity and multibehaviours is weaker for women under the MM2+ definition. However, this trend reverses when considering engagement with three SNAP multibehaviours and using the MM3+ definition, with a higher effect size observed for women compared to men. Thus, it is not surprising that a study of the benefits for life expectancy after engagement with SNAP as health-enhancing behaviours, found that women had better outcomes in all comparisons.

Through quantifying the complex relationship between multibehaviours and SNAP multibehaviours, the current review contributes to our understanding of complex, rather than singular, health phenomena, such as health behaviours (Prochaska, 2008) and morbidities (Van den Akker et al. 2000) and underlines the significance of such multidisciplinary research for health policy framework, which tend to be developed around treatment of single diseases (Shadmi, 2013). In this sense, the concern that arises from present review's pooled effect outcomes, for public health and current healthcare system is in alignment with those already known from other systematic reviews on multimorbidity prevalence (Violan et al. 2014), progression (Ryan et al. 2015), and mortality rates (Diederich et al. 2011). For example, in this current review, mortality rates that follow the presence of multimorbidity and SNAP multibehaviours, meets the assumption of biological plausibility of association between multimorbidity and mortality argued by Nunes et al. (2016) meta-analysis. In parallel with the present review's dose response association between multimorbidity and SNAP multibehaviours and mortality, Nunes et al.'s (2016) also found a gradient association in terms of the number of included morbidities, with stronger association for MM3+ (vs. MM2+) operational definition.

These findings support the arguments presented by individual studies on multimorbidity and multibehavioural inquiry (Loprinzi, 2015), suggesting that research on multiple health behaviour changes in preventative medicine should be the primary focus of healthcare systems' preventive measure (Prochaska et al. 2008). Therefore, by failing to embrace a comprehensive approach that incorporates a joint multimorbidity-multibehaviours framework as fundamental aspect of standard healthcare delivery, health policymakers perpetuate a fragmented healthcare system (Stumm et al. 2019)

that targets single lifestyle risk factors and organises healthcare services around monomorbid conditions (Agborsangaya et al. 2012). However, it may be extrapolated from the evidence of the current systematic review and meta-analysis, this narrow approach falls short of providing optimal care, whether in terms of primary or secondary prevention of multimorbidity. Moreover, it fosters an increasing reliance on interventions such as pharmaceuticals, which not only pose greater risks to patient safety (Mercer et al. 2016) but also contribute to the rise of polypharmacy and the heightened likelihood of adverse drug events. Such practices significantly undermine public health (Doos et al. 2014).

In short, the present review strengthens the case to move away from models based on "personal responsibility" (the idea that a person stands alone against the consequences of his/her bad lifestyle "choices" carrying all the burden of his/her ill health (Minkler, 1999). Pioneer thinkers have suggested that a better understanding of multiple health behavioural change (Prochaska, 2008) inquiry could lead to better designed future prevention strategies (Meader et al. 2014; Marengoni et al 2011; Violan et al. 2014) and more efficient health policy services for tackling multimorbidity (Loprinzi, 2015) or for delaying its detrimental trajectory (Kuluski et al. 2015).

Finally, similar with previous reviews (Diederichs et al. 2011; Fortin et al. 2012) and meta-analyses (Nunes et al. 2016) on multimorbidity, methodological issues limit the generalisability of findings. The absence of a "gold standard" measurement (Diederich et al. 2011) and varied compliance with the proposed 12CC threshold were major sources of heterogeneity on some of pooled outcomes.

3.4.3 Quality of the evidence

Quality of evidence was evaluated for seven meta-analytic outcomes using the GRADE methodology (Guatt et. al. 2011; Balshem et. al. 2011; Series et. al. 2011; Guatt et. al. 2013) (Table 4).

Table 4. Grade: Examining the SNAP health risk behavioural exposure to multimorbidity risk

Certainty assessment							Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
MM-MB Overall (assessed with: OR)										
7	observational studies	serious	serious	serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	**OR 1.650** (1.38 to 1.97)	**2 fewer per 1,000** (from 2 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
HR-MM-Overall (assessed with: HR)										
4	observational studies	not serious	not serious	not serious	not serious	dose response gradient	**HR 1.26** (1.18 to 1.34)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ High	IMPORTANT
Mortality in presence of MM (assessed with: HR)										
2	observational studies	not serious	serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	**HR 2.63** (2.09 to 3.29)	**3 fewer per 1,000** (from 3 fewer to 2 fewer)	⨁⨁⨁⨁ High	IMPORTANT
Women MM-MB (3HRB-MM+2)										
4	observational studies	serious	serious	serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	**OR 1.59** (0.90 to 2.80)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁◯◯ Low	IMPORTANT
Men MM-MB (3HRB-MM+2)										
4	observational studies	serious	serious	serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	**OR 1.45** (1.01 to 2.10)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁◯◯ Low	IMPORTANT
<12CC - MM-MB										

Certainty assessment							Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
4	observational studies	serious	serious	serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	**OR 1.88** (1.72 to 2.05)	**2 fewer per 1,000** (from 2 fewer to 2 fewer)	⨁⨁⨁⨁ High	IMPORTANT

>12cc - MM-MB

5	observational studies	serious	serious	serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	**OR 1.53** (1.17 to 2.01)	**2 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT

The quality of evidence ranged from moderate to high, with high-quality evidence primarily derived from cohort studies that investigated the temporal association between multimorbidity and SNAP multibehaviours, as well as subsequent mortality risk. This high quality was largely attributed to the detection of a dose-response association, coupled with minimal concerns regarding heterogeneity, imprecision, and indirectness in the pooled effect analysis. However, the high heterogeneity associated with the observational study design moderated the quality of evidence derived from the overall pooled effect of the association between multimorbidity and multibehaviours. Similar, justification was also applied when downgrading to moderate quality the evidence derived from both the meta-analytic outcomes observed for sex.

However, observational design, indirectness and inconsistencies among individual studies did not negatively influence the quality of evidence from studies that examined the threshold of ≥12CC when measuring multimorbidity risk. This was mainly due to the dose response association that accompanied the pooled effect outcomes of studies that examined the <12CC or the ≥12CC threshold.

3.4.4 Strengths and limitations

Strengths of the current review include implementation of a predefined protocol and the wide spectrum of meta-analytic evidence to quantify various multimorbidity-SNAP multibehaviours relationships. This was further strengthened by the identified dose response associations between the numbers of SNAP multibehaviours and multimorbidity risk for all multimorbidity definition (i.e., MM2+ and MM3+).

Limitations are also acknowledged. First, there was considerable heterogeneity associated with some of the pooled effects, mainly generated by the number of morbidities included in multimorbidity measurements. Second, possible confounding typically associated with cross-sectional designs should further be considered when interpreting outcomes. Third, other forms of heterogeneity that might have influenced the outcomes of the present review but could not be examined in meta-analyses, include: the population, unmeasured variation in morbidities (e.g., severity, progression)(Weis et al., 2014); how multimorbidity is measured (Willadsen et al., 2016); additional lifestyle risk factors (e.g., obesity) that were examined and possibly incorporated within combined multibehaviours measures; the inherent limitations of observational study designs (Weis et al. 2014).

3.4.5 Conclusion

This review synthesised evidence derived from individual studies on two increasingly common and complex health phenomena (multimorbidity – SNAP multibehaviours) that create a heavy burden on healthcare systems worldwide, providing both theoretical and clinical valuable knowledge. The central finding of a strong dose response association between multimorbidity - SNAP multibehaviours strengthens the case for a radical shift toward a framework where both preventive and clinical/epidemiological medicines are equally acknowledged (Prochaska, 2008) and multimorbidity and multibehaviours concepts are put at its centre (Loprinzi, 2015).

***

After systematically reviewing the literature and providing meta-analytical evidence on the association between multibehaviours and multimorbidity risk, the following chapter examines the aetiological effect of SNAP multibehaviours as pathogens to multimorbidity risk in a large sample of patients from three general practices in Staffordshire.

4. Examining the effect of multibehaviours on multimorbidity risk: A cross-sectional study

4.1 Introduction

Addressing multimorbidity entails a dual approach. Firstly, attention should be directed towards primary prevention to diminish the incidence of new cases of multimorbidity. Secondly, prioritising secondary prevention as the pivotal factor in multimorbidity prognosis ensures optimal management of existing multimorbidity.

SNAP-HRBs emerge as prime candidates due to their extensively studied role in preventing the individual chronic conditions (Dhalwani et al. 2017). However, their association with multimorbidity began to receive attention less than a decade ago (Marengoni et al. 2011), following calls from researchers for aetiological evidence of key determinants essential for the development of primary and secondary prevention measures (Violan et al. 2014).

Much of the research in this area has focussed on examining single SNAP-HRBs and multimorbidity, and generated mixed findings. For example, Fortin et al. (2014) did not observe an inverse (or protective) association between physical activity and multimorbidity among men aged 65–94 years. Responding to this inconclusive situation, Cimarras-Otal et al. (2014) and Dhalwani et al. (2016) both reported such an inverse dose-response association. Similarly, inconsistent results were also found with alcohol binge drinking (Han et al. 2018), and diet (Nepal et al. 2012).

While these findings regarding the focus on single SNAP-HRBs may be influenced by methodological or statistical artifacts, they also emphasise a subtle pragmatic limitation: the oversight of the synergistic effects that accompany their clustering (Griffin et al. 2014; Morris et al. 2016).

There is a need for greater understanding of the synergistic effects of SNAP-HRBs on multimorbidity risk, which transcends oversimplified analyses, and can lead to more clinically valuable outcomes (Griffin et Al. 2014; Morris et al. 2016). This includes recognising the increased likelihood of developing multimorbidity but also the potential for synergistic interventions targeting multiple SNAP-HRBs rather than individual behaviours (Pronk et al. 2004). Ultimately, this can inform the development of a

multimorbidity - multibehaviours theoretical and clinical framework able to guide the future research in specific inquiry (Loprinzi, 2015).

This becomes particularly significant when considering the findings from Randell et al. (2015) regarding primary care consultations attendees in the UK. Their study indicated that 95.5% of attendees were eligible for receiving health risk behavioural intervention, with almost half of them (43.6%) identified as suitable for multibehavioural interventions. However, only a handful of epidemiological studies, as outlined in the Chapter 3, have answered this call by exploring the combined and cumulative effect of SNAP-HRBs on multimorbidity risk.

The meta-analysis (Chapter 3) offered insights to address questions posed by Lee et al. (2009) regarding the quantification of the interrelation between multimorbidity and multibehaviours, such as multimorbidity-multibehaviours association varying with the number of SNAP multibehaviours and the operational definition of multimorbidity. Yet, there are still issues not well understood. The positive dose-response association between the number of SNAP multibehaviours and multimorbidity risk seems to intensify when the same number of SNAP multibehaviours is examined under multimorbidity definitions with stricter cut-offs. However, it remains uncertain whether this pattern persists with other types of multimorbidity definitions such as Complex multimorbidity (when three or more conditions affect at least three different organ systems).

Furthermore, stratified analyses investigating sex differences in multimorbidity risk remains puzzling. For example, among men, the threshold for a significant relationship between multimorbidity and multiple SNAP behaviours varied depending on the number of SNAPs involved (i.e., two or more health risk behaviours). Conversely, for women, the threshold was exclusively related to the operational definition of multimorbidity applied (i.e., MM3+). In contrast, de Almeida et al (2020) found that all SNAP-HRBs were statistically significant to the development of multimorbidity in men, but not in women.

Therefore, the aim of this study was to comprehensively investigate the association of SNAP-HRBs with multimorbidity risk, comparing the Complex multimorbidity definition against morbidity count definitions (MM2+ and MM3+), using stratified analyses by sex to further explore this complex area.

4.2 Method

4.2.1 Study design

This is the first of the two retrospective observational studies that focused on a multicentre data gathered between 2015 and 2018. Specifically epidemiologic studies examined the electronic health records (EHR) of a convenience sample of three general practices (GPs) in Staffordshire, UK, that used the EMIS web clinical system. The usage of EMIS system was considered an important prerequisite for two main reasons. Firstly, because it secures the existence of more accurate and holistic picture of patient's morbidities trajectory, allowing various healthcare practitioners from primary or secondary sector to view and contribute to patient's. However, EMIS enhances patient record accuracy through NHS Number matching, standardised data coding (SNOMED CT and Read Codes), and interoperability across healthcare settings (Sukriti et al., 2024). Secondly, because the data extraction from EMIS network is permitted only to an authorised-specialised personnel minimising possible, double counting, omissions or defaults, securing at the same time the access to an unadulterated data.

Commissioning Support Unit (CSU) of NHS Midland, and Lancashire was responsible for extracting the current dataset (Appendices 5-6), in co-operation with the present PhD researcher in summer of 2018. A mock data extraction exercise was performed before the official extraction to secure the correctness of the extracted data and possibly avoid double counting or any other omissions. Further support that was given by CSU team during the extraction process regards with the appropriate translation of Read codes (Appendix 7), the electronic thesaurus for clinical terms used by NHS since 1985, to morbidities of interest. This applied methodology addresses concerns experienced by similar studies (Abad-Díez et al., 2014; Prados-Torres et al., 2012) regarding with whether or not the GP personnel has the experience to use correctly the technology accompanied patients' EHR records.

The extracted data concerned all those registered with the participatory GPs between 2015 and 2018 that were age 18+ years and over. For each participant that met this criterion three different types of information were extracted by their EHRs.

4.2.2 Socio-demographic variables.

Socio-demographic data were extracted focusing on age, sex, ethnicity, and Lower Layer Super Output Areas (LSOA) of residence. LSOAs are based on small groups (three or four) of Output Areas (OAs) which is the lowest level of geographical area for census statistics comprising at the end, between 400 and 1,200 households that approximate to 1,000 - 3,000 people of resident population. Currently, there are 33,755 LSOAs in England that follow a pattern from the most deprived to the most affluent one. Each Lower-layer Super Output Area (LSOA) in England and Wales was used to ascertain deprivation based on the English Indices of Deprivation (MHCLG, 2019). This decision was made because the Index of Multiple Deprivation (IMD) offers a more comprehensive measure of relative deprivation for small areas, considering a wider variety of factors such as income, employment, health deprivation and disability, education, crime, barriers to housing and services, and living environment (MHCLG, 2019). Consequently, each LSOA is assigned a corresponding IMD score, which is ranked and utilised to derive deciles of deprivation, where 1 signifies the most deprived and 10 the least deprived. These deciles were then converted to quintiles for the present analyses, with Q1 representing the most deprived and Q5 the least deprived. The IMD serves as the official measure of relative deprivation in England and is integral to the suite of outputs comprising the Indices of Deprivation (IoD). Operating within an established methodological framework, the IMD broadly defines deprivation to encompass a wide range of an individual's living conditions. The IoD2019 integrates 39 separate indicators, organised across seven distinct domains of deprivation, which are combined and weighted to calculate the Index of Multiple Deprivation 2019 (Appendix 8).

4.2.3 Multimorbidity index

Since no standard approach exists regarding the measurement of multimorbidity (Adams et al. 2017; Harrison et al. 2014), the current study's methodology follows the one applied by Barnett et al. (2012) including a list of 40 morbidities (Appendix 9). This covers both the spectrum of physical and mental morbidities and as it has been shown in Chapter 3, met the minimum inclusion requirements posed by two systematic reviews (Diederichs et al. 2011; Fortin et al. 2014) as the core for any multimorbidity measurement. According to them, any multimorbidity investigation should at least

include 11 or 12 respectively of the most common chronic conditions (cancer, diabetes, depression, hypertension, myocardial infarction, chronic ischemic heart disease, heart arrhythmias, heart insufficiency, stroke, COPD, and arthritis).

Operationally, the two most commonly utilized operational definitions (MM2+ and MM3+) were selected based on suggestions derived from the influential systematic review by Fortin et al. (2012). Simply put, they recommended the cross-examination of both operational definitions, primarily due to the limited discriminatory ability of the more traditional MM2+ definition. For quick reference, please see Chapter 3, Section 3.1.

Additionally, a complex multimorbidity definition, which determines whether a person has acquired either two or more or three or more chronic conditions impacting at least three different organ systems, has been developed to increase the discriminatory value of multimorbidity operational definitions (Singer et al. 2019; Storeng et al. 2020).

Huntley et al. (2012), while assessing the predictive accuracy of the aforementioned traditional definitions alongside the alternative one of Complex multimorbidity, suggested an equally good performance. However, given the limited application of Complex multimorbidity definition within literature, they recommended the combined implementation of all three above-mentioned measurements to increase the validity of the identified outcomes. Following this recommendation the present study applied all three operational definitions of multimorbidity.

Furthermore, with the assistance of CSU personnel, the list of the 40 morbidities from Barnett et al.'s (2012) multimorbidity index has been adjusted to Cumulative Illness Rating Scale (CIRS) body systems, including cardiovascular, respiratory, visual, cancer, hepatic, gastrointestinal, mental, neurological, endocrine, sensory, renal, and musculoskeletal (see Appendix 9).

4.2.4 Multibehaviours

Finally, information was extracted that related to the four most common health risk behaviours (HRB): Smoking, Nutrition, Alcohol and Physical activity (SNAP). To get the most accurate picture regarding patient’s involvement with the SNAP health behaviours

and acknowledging the limitations around recording of this information in primary care, the EHR was used to extract information based on measurement of the behaviours (if present), and evidence of patients being given advice relating to changing these behaviours. These are detailed in turn:

- Smoking status was extracted from EHR as ‘current smokers’, ‘ex-smokers’, and ‘never-smokers’ (see Appendix 10). For pragmatic and theoretical reasons, these were regrouped into a binary categorisation as ‘ever-smoker’ and ‘never-smoker’. Practically, it was expected that the binary categorisation better captures the cumulative smoking exposure over time, which may be more relevant for assessing its association with multimorbidity than current or former status alone, and it would better facilitate the examination of associations of combined and accumulative SNAP-HRBs with multimorbidity risk. Additionally, many epidemiological studies examining the association between smoking and multimorbidity have used binary smoking categories (Hasse et al. 2015). While, methodologically, it is expected that the binary categorisation enhances both statistical power to detect significant associations between smoking status and multimorbidity, and helps to mitigate potential misclassification biases that may have been introduced to the system via the registration process and associated with self-reported smoking status, which may vary in accuracy across different population groups (Taylor et al., 2017). Healthcare providers advice such as ‘health education’ or ‘smoking cessation advice’ were categorised as ‘ever-smoker’ in binary coding.
- Nutrition was categorised as poor diet (meaning lack of regular fruits/vegetables per day and/or fat unhealthy diet), average diet (diet that has periodically both the characteristics of unhealthy and healthy diet) and healthy diet (that meets both the criteria of low-fat diet rich to vegetables and fruits) (Appendix 11). Again, for practical and statistical consistency, binary coding was applied to diet classifications. 'Poor' and 'average' diets were recoded as 'bad nutrition,' while 'good' diets remained unchanged. Healthcare provider advice was also considered. For example, recommendations such as 'patient advice about weight-reducing diet,' 'healthy eating advice,' and 'patient advice for low-cholesterol diet' were all categorized as bad nutrition (for a detailed list of advice categories, please refer to Appendix 11).

- Alcohol - intake was based on the consumption of alcohol units per week. As such, it was classified as ‘excessive alcohol usage’ when alcohol intake was greater than the 14 units per week, or ‘normal drinking consumption’ when did not exceed the 14 units per week or ‘never drinking’. The binary coding for this category involved recoding ‘normal drinking consumption’ and ‘never drinking’ as 'normal drinking,' while excessive alcohol usage remained unchanged. Healthcare providers' advice, such as 'Advice on alcohol consumption,' 'lifestyle advice regarding alcohol,' or 'alcohol health promotion,' among others, were all recoded as excessive alcohol usage (for coding on alcohol intake, refer to Appendix 12).
- Physical activity was classified based on the guidelines of 150 minutes of moderate activity or 60 minutes per week of vigorous activity (Appendix 13). Binary coding was conducted as follows: individuals initially classified as ‘moderately active’ or ‘inactive’ were recoded as ‘physically inactive’, while those originally labelled as ‘active’, or ‘meeting the recommended guidelines’, remained unchanged. Healthcare providers' advice, such as 'health education - exercise' or 'patient advice about exercise,' were all coded as physically inactive.

For decoding suggestions based on Read code system assistant from CSU team and other health specialists such as a PhD dietitian was obtained.

Extracted data were anonymous and as such no possible identification of participants was possible. More than that, current research obtained ethical approvals from both Staffordshire’s University Ethical Committee (Appendix 14) and the NHS Health Research Authority (East of England – Essex Research Ethics Committee) (Appendix 15).

4.2.4 Statistical Analysis

Frequency calculations provided a descriptive analysis of characteristics of the study population, and an estimation of the prevalence of all types of multimorbidity, the various morbidities included in multimorbidity measurement, as well as all SNAP health behaviours single or combined. Chi-square analyses were used to examine the association between multimorbidity and SNAP health behaviours, associations with socio-demographic variables, such as age, sex, and area of living (possible confounders

of the MM-SNAP association). Sequentially, - multivariate logistic regression models assessed the odds of acquiring MM (using each of the MM definitions of multimorbidity) by the engagement with any combined, and accumulative SNAPs. This was explored through unadjusted and adjusted models, and stratified by sociodemographic covariate of sex. Other types of stratified analyses, such as the socio-economic deprivation, were not undertaken. The decision was made solely based on methodological considerations. Although all relevant data was extracted and prepared for analysis, factors such as the heightened risk of reverse causality outcomes in the association between multimorbidity, multibehaviours, and the geographical area of residence, stemming from a highly skewed cohort, deterred the execution of specific analyses.

Finally, multiple imputation was applied to address the missingness problem overcoming the biases possible when a missing value(s) are detected (and cases excluded from analysis).

4.3 Results

4.3.1 Addressing the issues of missing data

The percentage of missing values ranged from zero (all variables that represent the included morbidities) up to 55.6% (nutrition variable). The rest examining SNAP-HRBs such as smoking, alcohol and exercise had missing values of 7.6%, 26.1% and 39.3%, respectively. For the demographic variables, these ranged from almost zero for deprivation to 23.4% for ethnicity, reaching the high missing rate of 85.6% for employment variable to a sample of 21.079 participants.

Given that variables with most missing data were demographic issues like employment and the SNAP-HRBs, but not patients' disorders, it is possible that there are inconsistencies in procedures during the registration of patients to primary care electronic system. Other reasons may be the reluctance of patients to share sensitive personal information (e.g., the amount of daily alcohol drinking), or lack of thorough follow up regarding the inclusion of adherence to SNAP guidelines.

Missing data problem was addressed using multiple imputation (MI) in SPPS. Specifically, by visually examining the existence or not of monotonicity in missing data (by inspecting the appearance of specific pattern), confidence was gained that values were missing at random since no such a pattern revealed (Appendix 16). To achieve the best possible

imputed value outcomes, all auxiliary variables were included within MI. As such, a Markov Chain Monte Carlo (MCMC) method by a logistic regression model was applied, since no monotonicity was found, and all included variables were categorical ones. Indicating 10 iterations for this process, SPSS generated five imputed data sets, whereby applying "Rubin's rules" a pooled dataset was produced (Hayati et al. 2015; Manly & Wella, 2015). Running a logistic regression to four SNAP-HRBs a reasonable comparison between imputed and observed valued was implemented. All statistical analyses were performed on the pooled imputed dataset.

4.3.2 Sociodemographic characteristics

Table 5 summarises the study population characteristics. Sex distribution showed similar proportions of the males and females in the study population (52.1% and 47.9%, respectively). The rest of the sociodemographic variables, when measured, were found to be highly skewed (see Appendix 17 for categorisation). Indicatively, the majority of the sample were classified as British/mixed British or White (84.7%), with those being classified as Arabs, Asians, and Blacks accounting for much smaller proportions (8.85%, 3.8% and 2.7% respectively). Regarding with the age variable, the younger age group of 18–45-year-olds was overrepresented, comprising almost half of the study population (48.7%). approximately one-third were aged 46-66 years (32.1%), and 19.2% were age 67 years or more. The particular age cut offs followed those regularly appear in multimorbidity studies (Agborsangaya et al. 2012; Violan et al.2013).

Table 5. Sociodemographic characteristics of participants

Groups	**N**	**%**	**95% CI**	
			Lower	Upper
Sex	21079			
Males	10986	52.1	51.4	52.8
Females	10093	47.9	47.2	48.6
Age groups				
18-45	10258	48.7	48	49.4
46-66	6773	32.1	31.5	32.7
67+	4048	19.2	18.7	19.7
Ethnicity				
White	8821	41.8	41.1	42.5

Groups	N	%	95% CI	
Mixed	9033	42.9	42.2	43.6
Asian	803	3.8	3.5	4.1
Black	566	2.7	2.5	2.9
Arabs/other	1856	8.8	8.4	9.2
Area of living				
most deprived	3,367	16.0	15.5	16.4
deprived	2,674	12.7	12.2	13.1
moderately deprived/affluent	2423	11.5	11.0	11.9
affluent	3905	18.5	17.9	19.0
most affluent	8710	41.3	40.6	41.9
HRBs				
0 HRB	81	0.4	0.3	0.6
ANY SNAP-HRB	20,998	99.6	99.4	99.6
SNAP-HRB 1	1,608	7.6	7.2	7.9
SNAP-HRB 2	6,114	29	28.3	29.6
SNAP-HRB 3	9,592	45.5	44.8	46.1
SNAP-HRB 4	3,684	17.5	16.9	18.0
Smoking				
smoker	5008	23.8	23.2	24.4
ex smoker	3105	14.7	14.2	15.2
non smoker	12966	61.5	60.8	62.2
Alcohol				
excessive	19463	92.3	91.9	92.7
normal	734	3.5	3.3	3.7
never	882	4.2	3.9	4.5
Physical Activity				
Inactive	3930	18.6	18.1	19.1
moderate inactive	3241	15.4	14.9	15.9
moderately active	7125	33.8	33.2	34.4
active	6783	32.2	31.6	32.8
Nutrition				
poor diet	8609	40.8	40.1	41.5
average diet	6133	29.1	28.5	29.7
heathy diet	6337	30.1	29.5	30.7
Morbidities				
AF	452	2.1	1.9	2.2
Heart Failure	202	1.0	0.8	1.1
Hypertension	3821	18.1	17	18
PVD	171	0.8	0.67	0.92
Stroke TIA	455	2.2	2	2.3
CHD	721	3.4	3.1	3.6
Asthma	2542	12.1	11	12
Bronchiectasis	94	0.4	0.3	0.4
Chronic Sinusitis	255	1.2	1.01	1.3
COPD	400	1.9	1.7	2
Blindness	137	0.6	0.4	0.7
Glaucoma	456	2.2	2	2.3

Groups	N	%	95% CI	
Cancer	427	2.0	1.8	2.1
Prostate Disorders	463	2.2	2	2.3
CLD	336	1.6	1.4	1.7
Constipation	409	1.9	1.7	2.08
Diverticular Disease	460	2.2	2	2.3
Dyspepsia	4026	19.1	18.5	19.6
IBD	1356	6.4	6.06	6.73
IBS	1340	6.4	6.06	6.73
Alcohol Problems	276	1.3	1.14	1.45
Anorexia or Bulimia	49	0.2	0.13	0.26
Anxiety	1571	7.5	7.14	7.85
Dementia	179	0.8	0.67	0.92
Depression	2727	12.9	12.44	13.35
Schizophrenia	179	0.8	0.679	0.92
Epilepsy	211	1.0	0.86	1.13
Migraine	236	1.1	0.95	1.24
MS	61	0.3	0.22	0.37
Parkinsons Disease	64	0.3	0.22	0.37
Diabetes	1260	6.0	5.679	6.32
Hearing Loss	2304	10.1	10.47	11.32
CKD	655	3.1	2.86	3.33
Painful Condition	1688	8.0	7.63	8.36
Psoriasis - Eczema	418	2.0	1.81	2.18
Rheumatoid - Arthritis	186	0.9	0.77	1.027
Thyroid	1239	5.9	5.58	6.21
0	9284	44.0	43.36	44.71
1	3719	17.6	17.12	18.15
2	3121	14.8	14.32	15.27
3	1988	9.4	9.03	9.82
4	1187	5.6	5.31	5.94
5	734	3.5	3.23	3.72
6	470	2.2	2.02	2.41
7	251	1.2	1.04	1.33
8	153	0.7	0.6	0.83
9	95	0.5	0.35	0.54
10	39	0.2	0.12	0.23
11	24	0.1	-0.6	0.15
12	10	0.0	-0.1	0.7
13	3	0.0	-0.1	2.9
14	1	0.0	-0.4	1.2
CC	9,284	44.0	43.3	44.6
MM2+	8076	38.3	37.6	39
MM3+	4955	23.5	22.9	24.1
Cmpx MM	4,025	19.1	18.4	19.5

HRB=Health Risk Behaviours; SNAP=Smoking, Nutrition, Alcohol, Physical Activity; CC=Chronic Condition; MM+2=Multimorbidity of 2+CC; MM+3=Multimorbidity of 3+CC; Cmpx MM=Complex Multimorbidity;

In relation to SNAP-HRBs, only the 0.4% of the total group of participants did not engage with any of the four SNAP-HRBs. Excess alcohol intake was the most common behavioural risk factor, rating at 92.3%. Poor nutrition and those ever-smoked (smoker and ex-smokers) followed with 40.8%, and 38.5% respectively, while physical (in)activity appeared with much lower rates of 18.6%. Multiple SNAP-HRBs, reached 92% with only 7.6% of study's population engaging with a single SNAP-HRB. The prevalence of the most often applied multimorbidity operational definitions were 38.3% for MM2+, 23.5% MM3+ and 19.1% for Complex MM. Finally, the mean number of chronic condition was 3.06 (SD=1.75).

Chi squares (Table 6) analyses showed that all single SNAP-HRBs (x^2=402.46 (2), p<.001 smoking; x^2=597.074 (4), p<.001 nutrition; x^2=27.424 (2), p<.001 alcohol; x^2=114.845 (3), p<.001 physical activity) were significantly associated with age, sex, and deprivation - (Table 2). Similar significant associations were also observed between the above-mentioned sociodemographic variables and multimorbidity (x^2=275.336 (1), p<.001 MM2+, x^2=156.268 (1), p<.001 MM3+ and x^2=29.698 (1), p<.001 Complex MM).

Table 6. Associations between sociodemographic variables, SNAP - HRBs and multimorbidity operational definitions

	Sex			Age			Area of living		
	x2	df	p value	x2	df	p value	x2	df	p value
Smoking	402.46	2	p<.001	784.171	4	p<.001	1304.648	8	p<.001
Nutrition	597.074	2	p<.001	1055.984	4	p<.001	2984.235	8	p<.001
Alcohol	27.424	2	p<.001	133.15	4	p<.001	87.064	8	p<.001
Physical activity	114.845	3	p<.001	411.601	6	p<.001	896.726	12	p<.001
MM2+	275.336	1	p<.001	4157.263	2	p<.001	141.215	4	p<.001
MM3+	156.268	1	p<.001	4298.82	2	p<.001	130.555	4	p<.001
Cmpx MM	101.784	1	p<.001	4361.397	2	p<.001	109.114	4	p<.001

Examining of standardised residuals emerged from chi-square analyses (Table 7) provide a useful insight to examine associations regarding with the interpretation of the outcomes from upcoming logistic regressions (Sections 4.3.3 & 4.3.4) as why specific analyses such as the examining of possible social patterning of multimorbidity-multibehaviours in relation to area of living was avoided. Specifically, the significant negative association observed among females, individuals aged 46-66 yrs. old and 67+, and those residing in the most affluent areas suggests that the prevalence of current smoking is primarily driven by young males living in the most deprived areas. This trend

is further evident when analysing associations among never smokers, where the opposite pattern is observed. However, when considering the ex-smoker parameter, an additional positive association emerges between smoking (as an ever exposure SNAP-HRB) and individuals aged 46-66 yrs. old and 67+, as well as those living in moderately deprived or affluent areas. This additional finding informs forthcoming analyses on the relationship between smoking and multimorbidity, potentially offsetting any existing inverse associations between them.

In terms of nutrition, adherence to a healthy diet is influenced by being female, aged 46-66 years old, and residing in less deprived areas. Conversely, poor dietary habits are associated with the age groups of 46-66 and 67+, as well as with residents of the most deprived areas. The profile of average dietary habits predominantly consists of males in the younger age group of 46-66 yrs. old, residing in any of the areas under examination except for those classified as moderately deprived or affluent.

Excessive alcohol consumption was significantly associated solely with the older age group of individuals aged 67+, with no significant associations observed with other parameters. Even among the younger age group of 18-45 yrs. old, which also exhibited a significant association, a negative correlation was found, suggesting that fewer individuals than anticipated were involved in excessive drinking.

Finally, physical inactivity exhibits significant associations with female sex, the older age group of 67+, and all levels of deprivation (from most deprived to moderate deprived and affluent). Additionally, moderate levels of inactivity are significantly associated with females aged 46-66 yrs. old who reside in affluent areas.

Examining the standardised residuals of the association between multimorbidity's operational definitions and sociodemographic variables (including age, sex, and deprivation), it was observed that across all operational definitions, females, older age groups, and residents of the top 20% most deprived and 20% of least deprived areas emerged as significant driving variables. These parameters yielded higher participant counts than expected. Conversely, lower-than-expected participant counts (resulting in negative significant associations) were found for males, individuals in the younger age group of 18-45, and those residing in areas of intermediate deprivation levels.

Table 7. Results of the analyses of the associations between sociodemographic variables, SNAP-HRBs and MM operational definitions (residuals)

	Smoking			Nutrition			Alcohol			Physical activity						
Groups	smoker	ex-smoker	never smoker	poor diet	average diet	healthy diet	excessive drinking	normal drinking	never drinking	inactive	moderately inactive	maderately active	active	MM2+	MM3+	Complex MM
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Sex																
Males	62.1***	58.6***	46.7***(-)	41.8	34.8***	23.4*** (-)	52.6	50.1	43.8***(-)	17.6** (-)	14.3** (-)	32.7	35.4***	44.9***(-)	44.4*** (-)	45.0*** (-)
Females	37.9***(-)	41.4***(-)	53.3***	39.8	22.9*** (-)	37.3***	47.4 (-)	49.9	56.2***	19.8**	16.6**	35.0*	28.7*** (-)	55.1***	55.6***	55.0***
Age																
18-45	62.2***	35.0***(-)	46.7**(-)	32.4*** (-)	35.5***	30.0	47.7*(-)	56.8**	64.2**	16.2*** (-)	15.39 (-)	32.0**(-)	36.5***	25.4***(-)	17.4***(-)	13.5*** (-)
46-66	28.7***(-)	36.3***	32.5	43.4***	24.4***(-)	32.2**	32.5	31.2 (-)	25.9***(-)	17.0**(-)	16.4*	35.6**	31.0 (-)	35.7***	33.6	32.8
67-107	9.1***(-)	28.7***	20.8***	57.8***	15.6***(-)	26.6***(-)	19.9*	12.0***(-)	10.0***(-)	27.6***	13.9**(-)	35.2	23.2***	38.9***	49.0***	53.8 ***
Area of living																
Most deprived	23.9***	23.1***	11.2***(-)	8.5***	26.0***	16.3	16.3	9.4***(-)	15.3(-)	25.8***	15.4(-)	12.9***(-)	13.8***(-)	17.3**	18.8***	19.2***
Deprived	17.8***	16.3***	9.8***(-)	8.5***(-)	22.1***	9.2***(-)	12.6	12.5(-)	15.3 *	17.4***	11.5(-)	10.8***(-)	12.5(-)	12.4 (-)	12.5	12.4(-)
Moderately deprived/afluent	12.4	12.9*	10.8*(-)	7.7 ***(-)	10.7(-)	17.4***	44.6	10.5 (-)	10.7(-)	13.5***	11.1(-)	8.6***(-)	13.5***	9.6***(-)	9.3***(-)	9.6***(-)
Afluent	19.0	18.7	18.3(-)	16.3***(-)	21.3***	18.9	18.0(-)	25.3***	5.8***	18.2(-)	21.2***	17.1**(-)	19.0	15.9 ***(-)	14.6***(-)	14.3 ***(-)
Most afluent	26.9***(-)	29.0***(-)	49.8***	58.9***	19.9***	38.1***(-)	41.7	42.2	3.4***(-)	25.2***(-)	40.8(-)	50.6***	41.2(-)	44.7***	44.8***	44.6***

4.3.3 Combined SNAP-HRBs

4.3.3.1 Overall

The outcomes of regression models, of dual combinations of SNAP-HRBs after adjusted for age, sex and areas of living are presented in Table 8. In short, all SNAP-HRBs combinations found to be significant predictors of all types of multimorbidity operational definitions, ranging from 15% higher chances for developing MM2+ if smoking combined with alcohol usage, to 75% increased chances for developing Complex MM when poor nutrition is combined with excessive alcohol usage. Generally, nutrition was found to be the key component of the most significant combined SNAP-HRBs associations at all operationally applied multimorbidity definitions.

Table 8. Unadjusted and Adjusted Odds Ratios for Incident Multimorbidity by combined SNAP-HRBs

SNAP-HRBs Combined	Unadjusted OR (95% CI)	Adjusted* OR (95% CI) by age, sex & IMD
MM2+		
Smoking - Alcohol	1.03 (0.97-1.09)	**1.15 (1.08-1.23)**
Smoking - Nutrition	**1.08 (1.02-1.15)**	**1.27 (1.18-1.37)**
Smoking - P.A.	**1.24 (1.16 (1.32)**	**1.23 (1.14-1.33)**
Nutrition - P.A.	**1.36 (1.28-1.44)**	**1.26 (1.19-1.35)**
Nutrition - Alcohol	**1.35 (1.28-1.44)**	**1.38 (1.29-1.47)**
P.A. - Alcohol	**1.55 (1.47-1.65)**	**1.21 (1.13-1.29)**
MM3+		
Smoking - Alcohol	**1.21 (1.14-1.30)**	**1.39 (1.29-1.50)**
Smoking - Nutrition	**1.28 (1.19-1.37)**	**1.54 (1.42-1.68)**
Smoking - P.A.	**1.49 (1.39-1.60)**	**1.50 (1.38-1.63)**
Nutrition - P.A.	**1.57 (1.48-1.68)**	**1.47 (1.37-1.58)**
Nutrition - Alcohol	**1.52 (1.41-1.63)**	**1.53 (1.42-1.66)**
P.A. - Alcohol	**1.78 (1.66-1.91)**	**1.34 (1.24-1.45)**
Complex MM		
Smoking - Alcohol	**1.21 (1.13-1.30)**	**1.36 (1.25-1.48)**
Smoking - Nutrition	**1.31 (1.21-1.41)**	**1.57 (1.43-1.72)**
Smoking - P.A.	**1.53 (1.42-1.65)**	**1.52 (1.39-1.66)**
Nutrition - P.A.	**1.70 (1.59-1.82)**	**1.60 (1.47-1.73)**
Nutrition - Alcohol	**1.60 (1.48-1.73)**	**1.62 (1.49-1.77)**
P.A. - Alcohol	**1.94 (1.79-2.09)**	**1.44 (1.32-1.57)**

As such for MM2+ the combination of nutrition-alcohol produced the higher outcome effects (adj. OR=1.38 95%CI 1.29-1.47) followed by the smoking-nutrition combination (adj. OR=1.27 95%CI 1.18-1.37). Smoking-nutrition was the most significant combination for MM3+ (adj. OR=1.54 95%CI 1.42-1.68) with marginal difference from the second which was the nutrition-alcohol combination (adj. OR=1.53 95%CI 1.42-1.66). For Complex MM, nutrition-alcohol again produced the high outcome effect of multimorbidity risk (adj. OR=1.62 95%CI 1.49-1.77) followed by the nutrition-physical inactivity combination (adj. OR=1.60 95%CI 1.47-1.72) with differential effect of 2%.

4.3.3.2 Stratified analyses by sex

Despite female sex being associated more than males for the most of the combined SNAP-HRBs (Table 9), when analyses were stratified by sex and adjusted for age and areas of living, a consistent pattern was observed only for MM2+ and Complex MM. For these two multimorbidity definitions, the only combination that produced an outcome effect that was higher for males than the females was physical inactivity-alcohol. Specifically, for MM2+, the effect was (adj. OR= 1.23 95% CI 1.12–1.36) in males versus (adj. OR= 1.19 95% CI 1.08–1.30) in females. For Complex MM, the effect was (adj. OR =1.60 95% CI 1.41–1.82) in males versus (adj. OR= 1.32 95% CI: 1.18–1.48) in females. The remainder showed more significant associations for females, with differential effects to range from 5% to 20% under MM2+ and from 2% to 27% for Complex MM, both for smoking-alcohol and smoking-nutrition combinations, respectively. For MM3+ the combined SNAP-HRB associations produced mixed result outcomes . Indicatively three combinations smoking-alcohol (adj. OR=1.40 95%CI 1.25-1.57 males VS adj. OR=1.38 95%CI 1.24-1.54 females); smoking-physical (in)activity (adj. OR=1.52 95%CI 1.35-1.71 males VS adj. OR=1.47 95%CI 1.31-1.65 females), and physical (in)activity-alcohol (adj. OR=1.49 95%CI 1.33-1.68 males VS adj. OR=1.23 95%CI 1.11-1.37 females) to affect male sex more than female. While the rest three such as smoking -nutrition (adj. OR=1.45 95%CI 1.29-1.63 males VS adj. OR=1.69 95%CI 1.50-1.91 females), nutrition- physical (in)activity (adj. OR=1.42 95%CI 1.27-1.59 males VS adj. OR=1.54 95%CI 1.40-1.70 females), and nutrition -alcohol (adj. OR=1.52 95%CI 1.34-1.72 males VS adj. OR=1.60 95%CI 1.45-1.77 females) was the other way around.

Another sex discrepancy was observed in relation to the most significant combined SNAP-HRBs. Nutrition-alcohol combination was the most important for both sexes, with all multimorbidity definitions. In females, nutrition remained the common dominator, where combining with smoking produce the second higher outcome from combined SNAP-HRB and multimorbidity risk. While in males, physical (in)activity and alcohol was their second higher outcome observed.

Table 9. Unadjusted and Adjusted Odds Ratios for Incident Multimorbidity by combined SNAP-HRBs stratified by sex

	STRATIFIED BY SEX			
HRBs	CRUDE		ADJ AGE - IMD	
	MALE	FEMALE	MALE	FEMALE
MM2+				
Smoking - Alcohol	**1.09 (1.00-1.18)**	**1.12 (1.03-1.23)**	**1.13 (1.02-1.24)**	**1.18 (1.07-1.31)**
Smoking - Nutrition	**1.09 (1.00-1.18)**	**1.34 (1.21-1.48)**	**1.20 (1.09-1.33)**	**1.40 (1.25-1.56)**
Smoking - P.A.	**1.31 (1.21-1.43)**	**1.29 (1.17-1.42)**	**1.19 (1.08-1.32)**	**1.27 (1.14-1.41)**
Nutrition - P.A.	**1.28 (1.18-1.38)**	**1.52 (1.40-1.64)**	**1.19 (1.09-1.31)**	**1.35 (1.24-1.48)**
Nutrition - Alcohol	**1.30 (1.19-1.42)**	**1.63 (1.50-1.77)**	**1.35 (1.22-1.50)**	**1.44 (1.32-1.57)**
P.A. - Alcohol	**1.57 (1.45-1.71)**	**1.48 (1.36-1.60)**	**1.23 (1.12-1.36)**	**1.19 (1.08-1.30)**
MM3+				
Smoking - Alcohol	**1.30 (1.18-1.43)**	**1.29 (1.17-1.42)**	**1.40 (1.25-1.57)**	**1.38 (1.24-1.54)**
Smoking - Nutrition	**1.25 (1.14-1.38)**	**1.58 (1.42-1.76)**	**1.45 (1.29-1.63)**	**1.69 (1.50-1.91)**
Smoking - P.A.	**1.64 (1.48-1.81)**	**1.49 (1.34-1.65)**	**1.52 (1.35-1.71)**	**1.47 (1.31-1.65)**
Nutrition - P.A.	**1.47 (1.34-1.62)**	**1.74 (1.59-1.90)**	**1.42 (1.27-1.59)**	**1.54 (1.40-1.70)**
Nutrition - Alcohol	**1.39 (1.25-1.55)**	**1.83 (1.66-2.00)**	**1.52 (1.34-1.72)**	**1.60 (1.45-1.77)**
P.A. - Alcohol	**1.94 (1.75-2.14)**	**1.60 (1.45-1.76)**	**1.49 (1.33-1.68)**	**1.23 (1.11-1.37)**
CompxMM				
Smoking - Alcohol	**1.28 (1.16-1.42)**	**1.28 (1.15-1.41)**	**1.35 (1.19-1.53)**	**1.37 (1.22-1.54)**
Smoking - Nutrition	**1.26 (1.14-1.40)**	**1.60 (1.43-1.79)**	**1.46 (1.28-1.66)**	**1.73 (1.52-1.97)**
Smoking - P.A.	**1.67 (1.50-1.85)**	**1.52 (1.36-1.69)**	**1.51 (1.33-1.72)**	**1.50 (1.32-1.70)**
Nutrition - P.A.	**1.56 (1.41-1.73)**	**1.90 (1.73-2.09)**	**1.52 (1.35-1.72)**	**1.69 (1.52-1.88)**
Nutrition - Alcohol	**1.39 (1.23-1.56)**	**1.99 (1.79-2.20)**	**1.53 (1.33-1.75)**	**1.75 (1.57-1.95)**
P.A. - Alcohol	**2.10 (1.87-2.35)**	**1.75 (1.58-1.95)**	**1.60 (1.41-1.82)**	**1.32 (1.18-1.48)**

4.3.4 Accumulative HRBs

Accumulation of SNAP-HRBs to one person showed a positive dose response association between the number of SNAP-HRBs and multimorbidity risk, that became stronger when the same number of SNAP-HRBs were examined under the MM2+, MM3+ and Complex MM (Table 10). As such the effect of any two SNAP-HRBs for Complex MM (adj. OR=1.50, 95%CI 1.33-1.69) was higher than the one for MM3+ (adj. OR=1.48, 95%CI 1.33-1.65), which in turn, was higher than the one for MM2+ (adj. OR=1.34, 95%CI 1.22-1.47).

Similarly, the same pattern was identified for the associations of any three or four SNAP-HRBs (adj. OR=2.17, 95%CI 1.89-2.4), (adj. OR=2.10, 95%CI 1.85-2.38), (adj. OR=1.57, 95%CI 1.42-1.73) for Complex MM, MM3+, and MM2+ respectively.

Table 10. Unadjusted and Adjusted Odds Ratios for Incident Multimorbidity by aggregated SNAP-HRBs

SNAP-HRBs Accumulative	Unadjusted OR (95% CI)	Adjusted* OR (95% CI) by age, sex & IMD
MM2+		
SNAP 2	**1.47 (1.39-1.56)**	**1.24 (1.16-1.32)**
SNAP 3-4	**1.80 (1.70-1.91)**	**1.52 (1.43-1.63)**
MM3+		
SNAP 2	**1.58 (1.48-1.68)**	**1.29 (1.20-1.39)**
SNAP 3-4	**2.27 (2.12-2.44)**	**1.88 (1.74-2.04)**
CompxMM		
SNAP 2	**1.63 (1.52-1.74)**	**1.31 (1.21-1.42)**
SNAP 3-4	**2.46 (2.27-2.66)**	**1.99 (1.82-2.18)**

4.3.4.1 Stratified analyses by sex

A clear dose response association within a group and positive gradient of outcome effect toward males emerged when analyses were stratified by sex and adjusted for age and deprivation (Table 11). Males had 18%, 31%, and 32% higher risk of vulnerability than females when engaging in any two SNAP-HRBs investigated under the MM2+, MM3+ and Complex MM, respectively. Despite the range of differences in outcome effects between sex decreasing to 4%, 22% and 23% with any three or four SNAP examined at MM2+, MM3+, and Complex MM, they remained significant between the sexes.

Table 11. Unadjusted and Adjusted Odds Ratios for Incident Multimorbidity by aggregated SNAP-HRBs stratified by sex

	STRATIFIED BY SEX			
SNAP-HRBs Accumulative	CRUDE		ADJ AGE - IMD	
	MALE	FEMALE	MALE	FEMALE
MM2+				
SNAP 2	**1.59 (1.47-1.73)**	**1.40 (1.29-1.51)**	**1.34 (1.22-1.47)**	**1.16 (1.06-1.26)**
SNAP 3-4	**1.79 (1.64-1.95)**	**1.96 (1.80-2.12)**	**1.57 (1.42-1.73)**	**1.53 (1.40-1.68)**
MM3+				
SNAP 2	**1.77 (1.61-1.95)**	**1.45 (1.33-1.58)**	**1.48 (1.33-1.65)**	**1.17 (1.06-1.29)**
SNAP 3-4	**2.34 (2.09-2.61)**	**2.36 (2.15-2.60)**	**2.10 (1.85-2.38)**	**1.81 (1.63-2.01)**
CompxMM				
SNAP 2	**1.81 (1.64-2.01)**	**1.50 (1.36-1.65)**	**1.50 (1.33-1.69)**	**1.18 (1.07-1.32)**
SNAP 3-4	**2.44 (2.16-2.76)**	**2.60 (2.34-2.89)**	**2.17 (1.89-2.49)**	**1.94 (1.73-2.18)**

4.4 Discussion

4.4.1 Main findings

Given the lack of a standardised approach to measuring multimorbidity risk, it was important to assess the combined effect and accumulated associations of SNAP-HRBs alongside traditional simple count measurements (MM2+, MM3+) and the alternative operational definition Complex Multimorbidity, as examined through the CIRS cumulative index. This comprehensive approach, while controlling for various socioeconomic and demographic variables, was regarded as essential for the emergence of more robustly validated outcomes, as highlighted by Huntley et al. (2012). Additionally, the stratification of analysis by sex shed light on an issue that puzzled multimorbidity research since its inception providing both clinically and theoretically valuable insights.

Three central outcomes transcend the results in this chapter.

- The establishment of the importance of all forms (combined and accumulative) of multiple SNAP-HRBs to multimorbidity risk, to all applied multimorbidity operational definitions, as reflected by their strong statistically significant outcome effects.
- The dose response associations that accompanied most of the interrelations between multiple SNAP-HRBs and multimorbidity, to all applied multimorbidity operational definitions
- The identification of a sex pattern interchangeably, analogous to multimorbidity definition,

The present study confirms and extends the evidence of newly emerging literature (see Chapters 2) regarding with the interrelationship between multibehaviours and multimorbidity, by demonstrating that all forms of multiple SNAP-HRBs significantly intervene in the risk of multimorbidity, regardless of its operational definition. Indicatively, the main evidence extracted from current analysis was that whether combined in specific dyads or accumulated in any form of two, three or all four SNAP-HRBs significantly predicted multimorbidity, for all applied types of multimorbidity operational definitions (MM2+, MM3+, Complex MM), with a positive dose response association. The only exception was the smoking-alcohol combination, which did not

produce a dose response effect (although marginal), but only for Complex MM. These findings help to confirm those of the systematic review-metanalysis (Chapter 3), which identified a positive gradient effect when the same types and forms of SNAP-HRBs examined multimorbidity definitions with higher or stricter cut-off points.

Many researchers have also mentioned the detection of such a dose response association pattern. For example, Adams et al. (2017), Dhalwani et al. (2017), Fortin et al. (2014), Katikireddi et al. (2017), all found a significant increase in odds ratio for developing multimorbidity with an addition of a SNAP-HRB. Loprinzi, (2015) showed the existence of an inverse dose response association, as a preventive mechanism to developing multimorbidity, when examining the accumulative health enhancing properties of three SN(A)P: no smoking, being physical active, and having a healthy diet.

The present findings have shown that all six possible SNAP-HRBs combinations generated significant outcome effects in relation to multimorbidity risk. This evidence challenges the outcomes of other studies that have also examined specific SNAP dyads. Loprinzi, (2015) for example, found significant predictive outcomes only when physical activity was combined with nutrition or smoking, and only for males; no significant association was identified for females for any possible SNAP combination. In the same trend Dhalwani et al. (2017) found significant predictive outcomes only for smoking when combined with physical activity or nutrition, but failed to identify any significance for alcohol when combined with physical activity or smoking. Better consistency observed when the accumulated associations of SNAP-HRBs with multimorbidity risk have been examined. Findings presented here align with studies of Adams et al. (2017), Agrawal et al. (2016), and Katikireddi et al. (2017) who all found significant effect and subsequent dose response associations between any type of accumulated SNAP-HRBs (e.g., two, three, four) and the development of MM2+. There was no harmonisation however, with Fortin et al. (2014) results for MM3+, where a threshold of two SNAP-HRBs in women and a corresponding threshold of four SNAPs-HRBs in men was needed before a significant effect on multimorbidity risk was observed. Shao et al. (2021), on the other hand, confirmed the present study's results, verifying the existence of a significant associations of all types of accumulative SNAP-HRBs alongside a dose response effect. Finally, the identification of the higher effect of accumulative SNAP-HRBs on Complex MM risk reported here, has no equivalent in literature. Nevertheless,

Shao et al. (2021) reported a significant association for all aggregated SNAP-HRBs on MM4+, which is a similarly strict criterion, compared with the more commonly used multimorbidity operational definition MM2+ and MM3+.

In sequence, all combined dyads of SNAP-HRBs were found to be important predictors of multimorbidity risk for all the applied operational multimorbidity definitions. The association regarding multimorbidity risk was found higher for female than the one of males for all dyads within MM2+ and Complex MM apart from the physical activity–alcohol combination where males were showing higher effect outcomes. As for the MM3+, findings were similar for both sexes, with females showing higher effects for all combined forms of nutrition while males were showing greater associations as it regards with smoking - alcohol, smoking – physical activity and physical activity -alcohol SNAP dyads.

Regarding with the accumulation of SNAP-HRB to multimorbidity risk, a sex pattern observed but, in contrast, males were showing higher significant associations than females with all forms of SNAP-HRBs accumulations and under all examining multimorbidity definitions. This evidence has no equivalent in literature since no sex pattern has been found by any other study that examined the same parameters. Indicatively, Fortin et al. (Fortin et al. 2014) found that MM3+ risk was significantly predicted when females had at least two SNAP-HRBs and males engaged in all four SNAP-HRBs.

4.4.2 Implications for research and practice

Generally, the findings of the present study answer the call for aetiological evidence on multimorbidity development (Violán et al. 2013; Marengoni et al. 2011). The complexity that emerges from the interrelations between all types of multimorbidity (MM2+,MM3+,Complex MM) and all forms of multiple SNAP-HRBs (combined, accumulative) provides further support for a more holistic management of care, that extends beyond the current medically monotone and monomorbid system. A basic characteristic of such a healthcare system will be the coalition of preventive and curative medicine toward a unified multibehaviours-multimorbidity theoretical and clinical framework (Loprinzi, 2015). This would better serve the healthcare system’s new

overarching goal of person-centre rather than disease focus provision of care. Via synthesis of interdisciplinary evidence, clinically valuable knowledge will emerge offering a new mode of explanation address the complexity posed by the new normalities of multibehaviours and multimorbidity. In turn, we will be able to address more efficiently the complex needs of people with multimorbidity.

Several challenges will accompany this effort. One of the most crucial challenges is to better align theory with reality. In short, it could be argued that while behavioural and clinical-epidemiological researchers thrive within their scientific specialities, the mainstream of articles and studies continues to examine the effects of single behaviours and/or single diseases. People experience complexities of the multibehaviours-multimorbidity and their interaction with the present provision of preventive and curative care. In 2008, Prochaska (2008) argued for the need to break down the disciplinary clinical and academic silos as prerequisite to effectively face the current challenges. This challenge remains. For example, instead of debating whether a single or multiple health behavioural change (MBHC) intervention is more effective (J. J. Prochaska et al. 2008) it could be more pragmatic to seek whether, within the framework of multimorbidity-multibehaviours, a consecutively or congruent MBCH interventions will be more appropriate for people with multimorbidity (Adams et al. 2017; Loprinzi, 2015) taking into consideration both the demands of everyday condition management (Freilich et al. 2020) and the severe time constraints faced by general practitioners/health care staff, limiting further the effectiveness of MBCH interventions (Prochaska, 2008).

Thus, a pivotal aspect within this person-centre provision of care that will be implemented within the multibehaviours-multimorbidity framework, is the development of trustful healing relationship between clinicians and patients, able to overcome series of barriers of unimpeded accessibility, self-management continuity, communication skills and cultural competence.

4.4.3 Limitations and strengths of the study

This is the first epidemiological study to comprehensively analyse both traditional count measurements (MM2+ and MM3+) alongside Complex multimorbidity in a

multimorbidity-multibehaviours inquiry. This synthesis not only enhances the validity of the study's outcomes, as demonstrated by Huntley et al. (2012) and Fortin et al. (2012), but also fosters deeper understanding. It underscores the importance of adopting an approach that is both clinically practical and relevant to policy, aligning with the principles advocated by Prochaska (2008).

A number of study limitations are recognised. First, the cross-sectional design precludes the investigation of the temporal sequence of the interrelation between SNAP-HRBs and the development of multimorbidity. Furthermore, the cross-sectional design prohibits any causality presumptions. Second, collection of data, especially SNAP-HRBs data may have resulted in some misclassifications due to the well-known weaknesses of the registration system and routine (or lack of) collection of such data within the general practices. For example, people may hide specific issues that they feel embarrassed, or other may be under-or-over estimated. Other misinformation may exist because people cannot perfectly define or recall the duration of their engagement with specific health behaviour e.g., physical activity. Finally, general practitioners' suggestions for lifestyle changes, that also be considered in the present study, may also contribute to possible misclassification due to possible over exaggeration e.g., alcohol suggestion reach the 92% of the current sample.

Strengths of the study include the large sample size, the multimorbidity index used that exceeds the minimum limit of the inclusion of the 12 most important chronic conditions and the use of electronic health records for extracting participants morbidities, as well as the implementation of multiple imputation.

4.4.4 Conclusion

While the high prevalence of all multimorbidity types (MM2+, MM3+, Complex MM) suggest the shift toward a more holistic approach that goes beyond the management of single disease, their significant interrelations with all forms of multiple SNAP-HRBs (combined, and accumulative) produce a complex situation that requires a shift of entire health-care system paradigm and the re-orientation of its priorities, goals, and targets. A basic characteristic of such system will be its person- rather than its disease-focus. Preventive and curative medicine should align toward healthcare systems overarching

goal, breaking down disciplinary silos and via the creation of multidisciplinary teams they will be able to address the complex needs of patients with multimorbidity.

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After analytically exploring the aetiological association between SNAP-HRBs and multimorbidity risk, the following chapter investigates the associative multimorbidity patterns and the multimorbidity-multibehaviour patterns through exploratory analysis, stratified by sex.

5. Multimorbidity-multibehaviours patterns in primary care population

5.1 Introduction

The increased prevalence of multimorbidity raises significant public health concerns (Jackson et al., 2016). These concerns extend from consequences of multimorbidity at the individual level, to challenges faced by the healthcare system, particularly in providing optimal care for people with multimorbidity (Sinnige et al. 2013; Cheryl et al. 2014). For instance, most guidelines used to treat multimorbidity are based on single diseases, posing challenges for healthcare providers to adapt to the needs of patients with multimorbidity without overburdening them or exposing them to the risks of adverse medication effects due to polypharmacy (Schäfer et al. 2010).

Over a decade ago, proponents of multimorbidity inquiry called for the redirection of research attention towards the production of clinically valued knowledge through the investigation of the association between key determinants of multimorbidity, such as the SNAP-HRBs, and multimorbidity (Marengoni et al. 2011). To achieve this, the analytical focus on multimorbidity – multibehaviours interrelationship turned to two types of analyses: aetiological and causal. According to the multimorbidity/comorbidity typology presented in section 1.8, this would permit a deeper understanding beyond the identification of a mere association between multimorbidity and its various factors. The first analytical focus, aetiological, was considered in Chapter 4 through examination of the aetiological multimorbidity. This prioritised the investigation of multibehaviours as pathological agents of multimorbidity using 40 morbidities that are associated with various organs and body-mind systems (Jakovljević & Ostojić, 2013).

The present chapter turns towards causal multimorbidity, and the quest for a shared underlying pathophysiological mechanisms such as chronic inflammation, oxidative stress, and metabolic syndrome that interconnects disease clustering (multimorbidity) between them and between common risk factor (multibehaviours) (Schäfer et al. 2010). To this end, researchers have embraced a data-driven methodology, of what Witty et al. (2020) called “cluster medicine”, to investigate multimorbidity patterns (Sukumaran et al. 2024). This approach helps to address the limitations of prevailing definitions of multimorbidity, such as MM2+, which are often criticised as overly simplistic, broad, and

lacking specificity (Abad-Díez et al. 2014). Based on the premise that morbidities can systematically correlate beyond randomness (Abad-Díez et al. 2014), it is expected that data-driven approaches, such as cluster analysis (CA) and exploratory factor analysis (EFA), can provide an insight into the synergetic effects of multibehaviours on specific multimorbidity patterns (Prado Torres et al. 2012).

By following this causal analytical route, the present chapter was dedicated to its pragmatic philosophy (Section, 2.3.1.2) aiming to contribute towards clinically useful knowledge to support the development of tailored multimorbidity guidelines (Sukumaran et al. 2024). This aims to prevent merely presenting ad hoc concomitant morbidities, such as those seen in concurrent multimorbidity analysis, or displaying simple statistically significant associations without causal justification, as observed in the simple cluster analysis between morbidities (Schäfer et al. 2010).

5.2 Methods

5.2.1 Study design and processes

This is the second retrospective observational study based on the multicentre data, retrieved from the electronic health records (EHR) of three general practices (GPs) in Staffordshire, UK. The choice to focus on EHR, as mentioned in the previous chapter, based on the evidence that suggest a better quality of the analysed data (Abad-Díez et al. 2014). In general, the extraction of socio-demographic data, multimorbidity index and SNAP-HRBs as proxy variables of unhealthy lifestyles, followed the pattern explained in previous epidemiologic study (sections 4.2.1, 4.2.2, & 4.2.3).

For the present study, the sample comprised all registered patients aged 18+ years, that have developed a multimorbidity (MM2+) from the list of 40 morbidities that Barnett et al. (2012) (Appendix 9), and were found to be engaged with at least two of Smoking, Nutrition, Alcohol and Physical activity (SNAP-multibehaviours). The accumulation of SNAP-multibehaviours, as described in Chapter 4, was calculated as a total sum of their dichotomised version (1 for engaging with the single SNAP-HRB and 0 for not engaging) that produced an overall score ranging from 0-4.

Ethical approval was gained from both Staffordshire's University Ethical Committee and the NHS Health Research Authority (East of England – Essex Research Ethics Committee) (Appendices 14 and 15).

5.2.2 Statistical analysis

Exploratory Factor Analysis (EFA) rather than Confirmatory Analysis (CFA) was applied to analyse the correlations between morbidities and reveal possible associative multimorbidity patterns of those suffering from MM2+ having found to be engaged with SNAP-multibehaviours. This approach was chosen due to the absence of strong theoretical expectations regarding the factor(s) structure, allowing for the exploration of patterns in the data before formulating formal hypotheses. Principal axis factoring with oblique rotation was chosen as a method for two reasons. Firstly, it has been acknowledged that the extracted patterns are limited, thus unable to fully explain the total variance when examining morbidities. Secondly, it's recognised that the extracted factors are often allowed to be associated with each other, a common occurrence in morbidity studies (Prados-Torres et al. 2012), even if this entails that a specific morbidity could be part of more than one multimorbidity pattern (Schäfer et al. 2010).

Allowing underlying factors to correlate with each other makes interpretation more complex. The only remedy is a thorough examination of factor loadings of both emerging matrices, namely the pattern and structure one. This is because, when factors are examined independently, factor loadings can simultaneously represent each factor's correlation and regression coefficients. This indicates the strength of the relationship between the variable and the factor, as well as how much of the variance the specific variable explains within that particular factor. This property is divided within the pattern and structure matrices (Field, 2009).

Permitting an underlying association between factors simply means that factor loadings in the pattern matrix provide information about the overall strength of the relationship between each variable on each factor (acting as a regression coefficient), while the information provided within the structure matrix focuses on the unique relationship between each variable and each factor after controlling for other factors (acting as a partial correlation) (Field, 2009). Thus, while the pattern matrix's interpretation is still

the given, a thoughtful consideration of the structure matrix is suggested, and the display of both matrices increases the transparency of researcher's interpretation.

To support further meaningful interpretations, only morbidities with factor loadings over the limit of 0.3 were included and interpreted as part of the emergent multimorbidity pattern (Osborne et al. 2011). Factors on their turn, they were extracted only when their eigenvalues exceeded the threshold of 1.0. The extracted factors represent the given multimorbidity patterns and their included morbidities factors loading represent their contributors (Field, 2009).

Due to the categorical nature of morbidity variables (0 for no morbidity and 1 for morbidity), tetrachoric correlation was applied. This is an accepted statistically heuristic approach assuming that despite being categorical (and as such violating assumptions of linearity and normal distribution) variables under investigation share an underlying continuum with normally distributed properties, e.g., an underlying latent causal morbidity progression that is not directly observable (Lorenzo-Seva & Ferrando, 2012).

The sampling adequacy for analysis is verified by Kaiser-Mayer-Olkin (KMO) measure. According to Field (2009), a minimum acceptable basis regarding with the goodness of fit is when KMO reaches or exceeds the threshold of 0.5. Progressively, values between 0.5 and 0.7 are considered as moderate while values between 0.7 and 0.8 are good, and values of 0.8 and 0.9 or above reflect great and superb goodness of fit, respectively. Finally, both Kaiser's criterion >1, and scree plot inflexion point were considered before judgment was made about the number of factors retained for final analysis. Given that the sample size of the current study for each investigation significantly surpassed the threshold of 250, any average communality exceeding 0.6 establishes Kaiser's criterion as a robust measure on its own (Field, 2009).To investigate the prevalence of the emergent multimorbidity patterns, the MM2+ operational definition of multimorbidity was applied, i.e., to allocate a person to a specific multimorbidity pattern, a minimum of at least two of factor's included morbidities was necessary. Furthermore, analysis was conducted separately for females and males. This is because the evidence from the multimorbidity literature (Abad-Díez et al. 2014) and results presented in previous Chapter 3, supports the assumption that sexes might be affected by different multimorbidity patterns. This suggests either the existence of different determinants or differences in magnitude of associations (Jackson et al. 2016). Finally, to achieve

clinically valuable outcomes, only morbidities with prevalence greater than 1% per sex were included in the study. Three certified doctors (one primary care physician and two hospital specialists) reviewed and verified the clinical value of the emergent multimorbidity patterns.

SPSS (version 28) was used for the Exploratory Factor analysis. However, data preparation was performed by the open-source software called Jamovi (as SPSS was unable to perform a tetrachoric correlation).

5.3 Results

5.3.1 Sample characteristics

Sociodemographic data for the entire sample population from the registered patients of three GPs were presented in section 4.3.2. Briefly, the entire population (*N*=21,079) had a roughly equal sex balance, with 52.1 % (*n*=10,986) males and 47.9% (*n*=10,093) females. Age was highly skewed with the younger aged group (18-45) representing almost the half of study's population (48.7%, n=10,258), followed by the middle-aged group (46-56 years, 23.1%, n=6,773) and sequentially by the older one (67+ years, 19.2%, n=4,048).

For the present analysis, the sample was restricted to 7,560 patients that had at least two morbidities (MM2+) and engaged with SNAP-multibehaviour. Sex remained well balanced, though slightly changed, with females comprising the majority group with 53.9% (*n*=4,079) and males comprising 46.1% (*n*=3482). However, compared with the entire sample population, the age parameter for the current study was different. The older age group (67+) constituted the majority comprising (40.1%, n=3,032) of study's sample, followed by the middle-aged group (46-66 years, 35.8%, n=2,707) and finally the younger one (18-45 years, 24.1%, n=1,820).

Table 12 shows the distribution of single morbidities for both sexes. Anorexia-Bulimia and Multiple sclerosis were excluded from the analysis, for both sexes since their prevalence was <1%. Parkinson's disease was also excluded for the same reason for females.

Table 12. Prevalence of morbidities by sex

	Males		Females		Total	
Morbidities	N	%	N	%	N	%
AF	246	7.1	177	4.3	423	11.4
Heart Failure	116	3.3	75	1.8	191	5.1
Hypertension	1628	46.8	1665	40.8	3293	87.6
PVD	118	3.4	49	1.2	167	4.6
Stroke TIA	238	6.8	203	5.0	441	11.8
CHD	496	14.2	209	5.1	705	19.3
Asthma	854	24.5	1059	26.0	1913	50.5
Bronchiectasis	38	1.1	45	1.1	83	2.2
Chronic Sinusitis	79	2.3	114	2.8	193	5.1
COPD	206	5.9	178	4.4	384	10.3.
Blindness	58	1.7	68	1.7	126	3.4
Glaucoma	203	5.8	204	5.0	407	10.8
Cancer	166	4.8	186	4.6	352	9.4
Prostate disorder	424	12.2	n/a	n/a	424	12.2
CLD	139	4.0	143	3.5	282	7.5
Constipation	151	4.3	215	5.3	366	9.6
Diverticular disease	146	4.2	266	6.5	412	10.7
Dyspepsia	1687	48.5	1759	43.1	3446	91.6
IBD	442	12.7	510	12.5	952	25.2
IBS	296	8.5	703	17.2	999	25.7
Alcohol problems	144	4.1	77	1.9	221	6.0
Anorexia-Bulimia	3	0.1	36	0.9	39	1.0
Anxiety	454	13.0	834	20.5	1288	33.5
Dementia	66	1.9	96	2.4	162	4.3
Depression	799	23.0	1440	35.3	2239	58.3
Schizophrenia	65	1.9	75	1.8	140	3.7
Epilepsy	92	2.6	86	2.1	178	4.7
Migraine	34	1.0	117	2.9	151	3.9
MS	11	0.3	34	0.8	45	1.1
Parkinsons Disease	34	1.0	22	0.5	56	1.5
Hearing Loss	973	28.0	857	21.0	1830	49
CKD	285	8.2	338	8.3	623	16.5
Painful condition	584	16.8	937	23.0	1521	39.8
Psoriasis & Eczema	137	3.9	165	4.0	302	7.9
Rheumatoid Arthritis	43	1.2	123	3.0	166	4.2
Diabetes	644	18.5	486	11.9	1130	30.4
Thyroid	210	6.0	753	18.5	963	24.5

5.3.2 Multimorbidity Patterns

5.3.2.1 Females

A principal axis factoring (PAF) with oblique rotation (Oblimin) was conducted on 34 morbidities. The sampling adequacy for analysis was verified by Kaiser-Mayer-Olkin measure. The KMO=0.808 was of great magnitude according to Field (2009). Bartlett's test of sphericity x^2 (105)=305.77, p<.001, indicated that correlations between items were sufficiently large for PAF. Analysis was run to obtain the eigenvalues for generating factors from the data. Three factors had eigenvalues over Kaiser's criterion of 1 and collectively explained 56.69% of the variance. The scree plot (Figure 5) showed an inflexion that merely justify the retaining of three factors contradicting the Kaiser's criterion. Examining the Kaiser's average communality, it was found to be 0.62, which is larger than the threshold of 0.6 limit that has been set for samples size above 250 people (Field, 2009). Therefore, all three factors were retained. Table 13 and Table 14 shows the factor loadings for both pattern and structure matrices after the rotation.

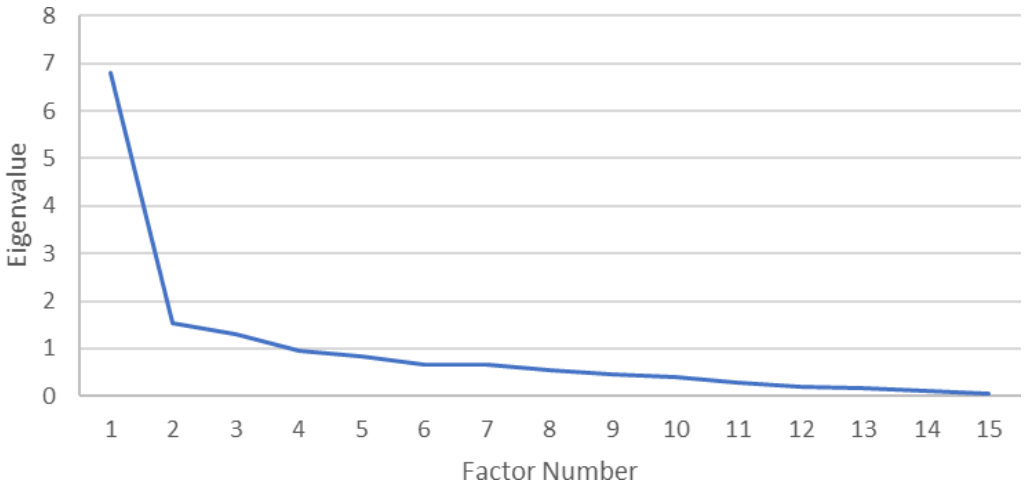

Figure 5. Scree plot for Females

The items clustered under three factors for females. Factor 1 (42.97%), under the unified label of **Cardiometabolic and neurovascular spectrum disorders**, was determined by the associations between coronary heart disease, atrial fibrillation, hypertension, peripheral vascular disease, chronic kidney disease, stroke and transient ischemic attack, diverticular disease, diabetes, dementia, and cancer. Factor 2 (8.08%) that was

labelled as **Respiratory conditions**, represented by COPD and bronchiectasis. Factor 3 (5.63%) was label as **Sensory impairment** and comprised by blindness, glaucoma, hearing loss and dementia.

Table 13. Pattern Matrix -Factor score for females multimorbidity patterns

	Factor 1	Factor 2	Factor 3
	Cardiometabolic and neurovascular spectrum disorders	**Respiratory conditions**	**Sensory impairment**
Coronary Heart Disease	**0.924**		
Atrial fibrillation	**0.828**		
Hypertension	**0.794**		
Peripheral Vascular Disease	**0.710**		
Chronic Kidney disease	**0.705**		
Stroke and transient ischemic attack	**0.702**		
Diverticular disease	**0.614**		
Diabetes	**0.546**		
Dementia	**0.440**		**0.400**
Cancer	**0.359**		
COPD		**0.820**	
Bronchiectasis		**0.787**	
Blindness			**0.790**
Glaucoma			**0.686**
Hearing loss			**0.445**

Table 14. Structure Matrix -Factor score for females multimorbidity patterns

	Factor 1	**Factor 2**	**Factor 3**
	Cardiometabolic and neurovascular spectrum disorders	**Respiratory conditions**	**Sensory impairment**
Hypertension	0.908		0.662
Chronic Kidney disease	0.897	0.350	0.705
Atrial Fibrillation	0.852	0.325	0.475
Coronary Heart Disease	0.824		0.392
Stroke and transient ischemic attack	0.752		0.490
Dementia	0.689		0.661
Peripheral Vascular Disease	0.659		
Diverticular disease	0.635		0.380
Diabetes	0.624		0.457
Cancer	0.396		
COPD		0.829	
Bronchiectasis		0.791	

Blindness	0.433		0.786
Glaucoma	0.415		0.704
Hearing loss	0.353		0.503

Almost quarter of the sample (25.4%) belonged to at least one of these patterns with prevalence ranging from 21.4% for the cardiometabolic-neurovascular pattern, to 3.2% for the sensory impairment one and 0.4% for the respiratory conditions.

5.3.2.2 Males

A principal axis factoring (PAF) with oblique rotation (Oblimin) was conducted on 35 morbidities. The sampling adequacy for analysis was verified by Kaiser-Mayer-Olkin measure. The KMO=0.680 found to be of good magnitude according to Field, (2009). Bartlett's test of sphericity x2 (105)=280.503, p<.001, indicated that correlations between items were sufficiently large for PAF. An analysis was run to obtain the eigenvalues for generating factors from the data. Five factors had eigenvalues over Kaiser's criterion of 1 and in combination explained 61.75% of the variance, but the scree plot (Figure 6) displayed inflexions that did not support retention of all factors. Given that Kaiser's average communality of 0.68 exceeded the threshold of 0.6 (set for samples sizes >250), five factors were retained (Field, 2009).

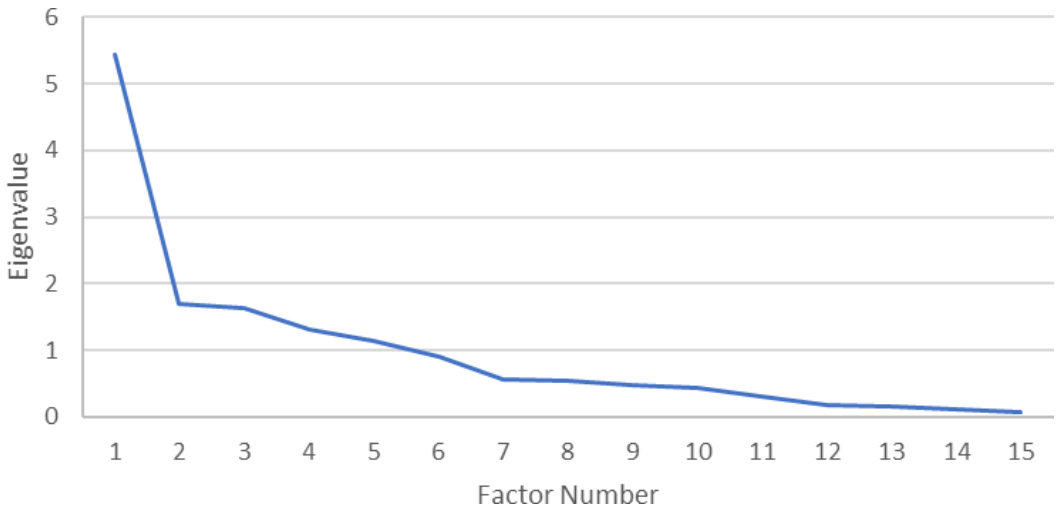

Figure 6. Scree plot for Males

Table 15 and Table 16 shows the factor loadings for both pattern and structure matrices after the rotation. Factor 1 (34.10%), under the unified label of **cardiometabolic and**

vascular was determined by the associations between diabetes, coronary heart disease, hypertension, peripheral vascular disease, dyspepsia, and chronic kidney disease. Factor 2 (9.19%) was labelled as **Genitourinary tract disorders** represented by Prostate disorders, cancer, and diverticular disorder. Factor 3 (8.20%) termed as **Respiratory and vision spectrum disorders** and comprised by bronchiectasis, COPD, blindness, peripheral vascular disease. Factor 4 (5.70%), **Ocular spectrum disorders**, included glaucoma, blindness, and cancer. Finally, Factor 5 (4.54%) **Neurovascular and gastro-renal syndrome** included stroke and transient ischemic attack, dementia, chronic kidney disease and dyspepsia. Forty-three per cent of the sample could be assigned to at least one of these multimorbidity patterns with prevalence of 40.1% for the metabolic cardiovascular pattern, 18.7% for the ocular spectrum diseases, 9.1% for the neurovascular and gastro-renal syndrome, 3.3% for the neoplasms with gastrointestinal pathways, and 1.4% for the respiratory and vision pattern.

Table 15. Pattern Matrix -Factor score for males multimorbidity patterns

	Factor 1	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**
	Cardiometabolic and vascular	**Genitourinary tract disorders**	**Respiratory and vision spectrum disorders**	**Ocular spectrum disorders**	**Neurovascular and gastro-renal syndrome**
Diabetes	**0.789**				
Coronary Heart Disease	**0.721**				
Hypertension	**0.649**				
Peripheral Vascular Disease	**0.526**		**0.314**		
Dyspepsia	**0.498**				**0.456**
Chronic Kidney disease	**0.488**				**0.366**
Prostate disorders		**0.860**			
Cancer		**0.654**		**0.364**	
Diverticular disease		**0.575**			
Bronchiectasis			**0.762**		
COPD			**0.623**		
Glaucoma				**0.685**	
Blindness			**0.368**	**0.524**	
Stroke and transient ischemic attack					**0.634**
Dementia					**0.632**

Table 16. Structure Matrix -Factor score for males multimorbidity patterns

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Cardiometabolic and vascular	Genitourinary tract disorders	Respiratory and vision spectrum disorders	Ocular spectrum disorders	Neurovascular and gastro-renal syndrome
Coronary Heart Disease	0.841	0.395			0.623
Hypertension	0.777	0.361		0.383	0.375
Diabetes	0.746				
Chronic Kidney disease	0.697	0.415	0.347	0.315	0.580
Peripheral Vascular Disease	0.659		0.445		0.320
Dyspepsia	0.576				0.564
Prostate disorders		0.915		0.313	0.451
Cancer		0.718		0.470	0.306
Diverticular disease		0.548			
Bronchiectasis			0.727		
COPD	0.405		0.683		
Glaucoma				0.703	
Blindness	0.407		0.428	0.572	
Stroke and transient ischemic attack	0.403			0.419	0.729
Dementia					0.623

5.4 Discussion

Advanced statistics provide us with a means to manipulate the complexity associated with the non-indexing multimorbidity (Cornell et al. 2009) by reducing it into meaningful formations, otherwise called associative multimorbidity patterns (Prados-Torres et al., 2012). The present analysis revealed eight patterns: five for males (metabolic-cardiovascular, genitourinary track disorders, respiratory and vision spectrum disorders, ocular spectrum disorders, and neurovascular – gastro-renal syndrome) and three for females (cardiometabolic and neurovascular spectrum disorders, respiratory conditions, and sensory impairments). The revelation of clinically stable multimorbidity patterns, where SNAP-HRBs could be regarded as key etiological determinants of multiple multimorbidity patterns, was the central narrative of the present study, and a first in this field of inquiry. The main findings are summarised and considered in the context of the literature.

5.4.1 Multimorbidity patterns

Only the pattern for cardio-metabolic-vascular was common to males and females, although with noticeable differences, though in their manifestations. The remaining identified patterns did not match across. Consequently, only the cardiometabolic (neuro)vascular pattern will be presented comparatively to both sexes. The remaining multimorbidity patterns are presented separately for each sex group.

5.4.1.1 Cardiometabolic- (neuro) vascular

This is the only matchable pattern between sexes. It shared the highest number of morbidities and had the highest prevalence for both sexes: 40.1% in males, which was twice that in females (21.4%).

The clinical value of the specific pattern is well acknowledged in medical literature encompassing morbidities that usually co-exist within a complex network of pathological pathways where chronic inflammation and insulin resistance are common dominators: diabetes, coronary heart disease, atrial fibrillation, hypertension, chronic kidney disease, peripheral vascular disease, stroke and transient ischemic attack, dyspepsia, diverticular disease and dementia (Defronzo, 2009; Hansson, 2005; Shoelson et al. 2006).

Indicatively coronary heart disease (CHD) is closely related to peripheral vascular disease (PVD) and hypertension (Benjamin et al. 2019), and has a bidirectional relationship with chronic kidney disease (CKD) and together, they are included among the highest risk factors for cardiovascular events (Sarnak et al. 2003). Additionally, diabetes is associated with CHD, PVD, stroke (Rawshani et al. 2018), diverticular disease (Wittström et al., 2022), cognitive decline (Zheng et al. 2018) and dementia. In turn, dementia is associated with cardiovascular diseases and hypertension (Ramanathan et al., 2020). Hypertension, is an important risk factor for both PVD (Makin et al. 2001) and CKD (Buffet and Ricchetti, 2012), alongside diabetes(Jha et al. 2013). Finally, while cancer has been associated with many of the included morbidities like diverticular (Zhang et al., 2023), cardiovascular diseases (Yeh et al. 2022), diabetes and CKD (Hartmann et al. 2012), as part of the cardiometabolic-vascular multimorbidity pattern, it was featured only for females in these analyses.

Furthermore, the progressive pathophysiology related to most included morbidities followed the expected pattern identified in literature (Prados-Torres et al., 2012). As it regards the age parameter, the older group (67+) for both sexes, was the one that suffered most, albeit females (75.6%) were affected more than males (62.2%). Conversely, the influence of the specific multimorbidity pattern was more evident in males (34.8%) than females (21.7%) in the middle-age group (46-66 years).

Evidence from numerous studies clearly implicates various SNAP-HRBs as key modifiable determinants for most morbidities included within the specific multimorbidity pattern. Specifically, Hackshaw et al., (2018) meta-analysis showed that even minimum smoking is related to developing CHD, while Lee et al., (2012) found that a lack of physical activity accounts for 6% of CHD incidents. Similarly Bhupathiraju and Tucker (2018) have clearly stated the preventative nature of healthy diet, minimising the risk for CHD. In conclusion, it is also noteworthy to mention the contribution of SNAP-HRBs to the development of CHD. Despite Zhao et al.'s (2017) meta-analysis not revealing a positive association between moderate alcohol consumption and CHD, they did find that former drinkers exhibit an increased risk of developing CHD.

Similarly, the influence of SNAP-HRBs has also been shown in the development of:

- CKD where for example, strong associations found for smoking behaviour (Orth, 2002) and low-protein, low-phosphorous diet (Barsotti et al. 1996).
- Dementia where an association with SNAP-HRBs was observed (Fulton, 2022; Singh et al., 2014)with some suggesting (Maddatu et al. 2017) SNAP-HRBs are among the top risk factors (Ramanathan et al. 2020).
- PVD where studies have identified the long term effects of poor nutritional habits (Nosova et al. 2015) and alcohol consumption (Ronksley et al. 2011)
- Diverticular diseases and especially the protective associations emerged from physical activity (Simrén, 2002) or high fiber and vegetarian diets (Piscopo and Ellul, 2020)
- Stroke where SNAP-HRBs in conjunction with diabetes, hypertension psychological and cardiac causes account for more than 90% of the incidences.

- Diabetes and hypertension where SNAP-HRBs are considered the key contributors for their development (Baliunas et al. 2009; Halperin et al. 2008; Lee et al. 2012; Maddatu et al. 2017)

5.4.2 Females

5.4.2.1 Respiratory conditions

This pattern, albeit accounting for only 0.4% of the sample, its clinical value is noted because it highlights the commonalities between COPD and Bronchiectasis. The two main morbidities that involved with the progressive damage of the of the airways (McDonough et al. 2011) having clinical symptoms of heavy cough, sputum production, recurrent respiratory infections, and dyspnea (Chalmers et al. 2014). The overlapping of these two conditions has been identified by several studies suggesting a unified preventive approach and management (Patel et al. 2004).

Literature has convincingly shown SNAP-HRBs as key modifiable risk factors to both abovementioned morbidities (Tuder and Petrache, 2012). Specifically, smoking (Rabe et al. 2007) and excess alcohol (Sisson, 2007) have been found to increase the risk of developing the morbidities included in the respiratory diseases pattern while physical activity can help to prevent the development of respiratory disease, and comorbidities (Choi et al. 2022). Furthermore, Muralidharan et al. (2023) examining the combined effects of smoking, excessive alcohol consumption and physical activity reported a synergistic impact on the development of progression of respiratory diseases.

A clear indication about the progressive age-related deleterious effect of SNAP-HRBs on the development of this specific pattern was identified in the pattern's prevalence rates, where the older aged group (67+ years) accounted for the 73.3%, the middle-age group (46-66 years) comprised 20% and the younger group accounted for 6.7%.

5.4.2.2 Sensory impairment

This is a term used by several researchers (Lin FR et al. 2013) but also WHO (WHO, 2021) referring to a range of conditions the affect sensory functions such as glaucoma, dementia, and hearing loss. It accounted for the 3.2% of study's female population while its presence was most prominent in the oldest age group 67+ year (86.3%). However, a

clear indication is that the onset of the accumulative impact of SNAP-multibehaviours on sensory impairment may be rooted to middle-age, since the 13% of those in middle-age group (46-66) found to have developed the specific multimorbidity pattern in comparison to only 0.8% of younger aged group (18-45). Several studies have evidenced the strong associations between the aforementioned morbidities (Gupta et al. 2021; Keenan et al. 2015; Nucci et al. 2015; Wipt and George, 2008a). Furthermore, etiological factors that have been suggested, apart from age-related biological pathways (Coleman and Miglior, 2008; Loughrey et al., 2014; Wipt and George, 2008) regarded those of chronic inflammation and vascular function (Chakravarthy et al. 2010), implicating the contribution of SNAP-HRBs to the development and progression of pattern's morbidities.

Several studies have provided evidence supporting this argument. For example, smoking has been found to have strong association with dementia (Peters et al. 2008), age-related macular degeneration, the leading cause of severe and irreversible vision loss (Chakravarthy et al. 2010; Thornton et al. 2005), primary open-angle glaucoma (Jain et al. 2017), and hearing loss (Agrawal et al. 2009; Wipt and George, 2008a). Additionally, excessive alcohol usage has been found to increase the risk of hearing loss (Park and Suh, 2019; Sowalsky, 2021) and dementia (Ballard and Lang, 2018). Nevertheless while evidence for glaucoma is unclear (Kang et al. 2007), a recent meta-analysis (Stuart et al. 2022) found a borderline though significant association between excessive alcohol usage and glaucoma. Finally, the identification of health beneficial properties of physical activity to protect against the development of age-related degeneration (McGuinness et al., 2017) and its progression (Seddon et al. 2003) support the argument further regarding the impact of SNAP-HRBs for this sensory impairment pattern.

5.4.3 Males

5.4.3.1 Genitourinary tract disorders

This pattern is among those characterised as sex specific, affecting 3.3% of the male sample population (with multimorbidity that have engaged with SNAP multibehaviour). The title given to the specific pattern is an accepted medical term (American Urological Association, 2021; European Association of Urology, 2021) used to unify morbidities and cancers that affect the organs of urinary and reproductive system, including prostate gland (prostate disorders) and colon (where diverticular disease

occurs) (Zhang et al. 2023). Depending on the study's sample, and related literature, middle-age seems to be the onset point (McVary et al. 2011; Piscopo and Ellul, 2020; Plaskon et al. 2003). Within this study the middle-aged group (46-66) accounted for 19.3% of those that have developed the specific multimorbidity pattern with the older group (67+) accounted for the rest 80.7%.

The present findings align with the literature (Piscopo and Ellul, 2020) and also found that, apart from age, SNAP-HRBs seem to have an important role in prevention, development and progression of the included morbidities. Evidence, albeit based on single SNAP-HRBs, supports that argument. For the development and progression of benign prostatic hyperplasia, smoking emerges as a significant factor (Platz et al. 1999). Additionally, a healthy diet plays a crucial role by influencing its pathophysiology (Espinosa, 2013) and associated with prostatic growth (Russo et al. 2021). Evidence on alcohol consumption is mixed, mainly depending on the amount and pattern of drinking. Some studies have identified detrimental effects of alcohol on benign prostate hyperplasia, while others did not (Parsons and Im, 2009). For prostate cancer, a dose-response association with pack-years of smoking (Huncharek et al. 2010; Plaskon et al. 2003) and amount of alcohol consumption has been revealed (Zhao et al. 2016; Zuccolo et al. 2013). Finally, while on the one hand being smoker increases the risk for developing diverticulitis by 46% in comparison to non-smokers as a current metanalysis showed (Wijarnpreecha et al. 2022), on the other being physically active (Wipt and George, 2008b) or having diet higher in fiber and vegetables (Crowe et al. 2011), were found to be protective factors, for males of middle age or older.

5.4.3.2 Respiratory and vision spectrum disorders

This pattern accounted for 1.4% of the sample's male population indicating a unified framework that encompasses the diseases of bronchiectasis, chronic obstructive pulmonary disease (COPD), blindness and peripheral vascular disease (PVD). The main emphasis regards the impact of those morbidities on multiple organ systems and highlights the significance of understanding the possible underling mechanism and their common risk factors. For example, COPD and Bronchiectasis are both chronic respiratory diseases (Chalmers and Chotirmall, 2018) with evidence to suggest that they often coexistence (Patel et al. 2004). Their main difference is that, while bronchiectasis

primarily affects the larger airways, COPD primarily affects the smaller airways(Rabe et al. 2007). Blindness, refers to the loss of visual function that may arise from various causes (Bourne et al. 2013). Respiratory (Mikaeili et al. 2015) and vascular diseases (Delaney W V Jr, 1993) are regarded among those causes, mainly be due to their subtle and often overlooked interconnection (Houben-Wilke et al. 2017). The present study indicated that age is a key parameter, with 91.3% of those who have developed the specific multimorbidity patterns belonging to the oldest age group (67+ years). The remainder (8.7%) were in the middle age (46-66) group, with none from the youngest group (18-45 years).

Several studies have also shown the effect of SNAP-HRBs as independent modifiable risk factors to the development and progression of the included morbidities alongside other common risk factors like genetic predisposition and chronic inflammation (Chalmers and Chotirmall, 2018). Smoking, in particular, is well-established as the most preventable risk factor for both respiratory (Kaushik et al. 2004; Laniado-Laborin, 2009) and peripheral vascular diseases (Wang et al. 2021), while furthermore, has been found to contribute to age-related macular degeneration (AMD), the leading cause of blindness in older adults (Thornton et al. 2005). On the contrary physical activity has been found to be a crucial protective factor for developing COPD (Waschki et al. 2011) or peripheral vascular disease (Rashighi and Harris, 2017). Finally, evidence regarding with alcohol seems to depend on the amount and pattern of drinking (Piano, 2017). While on the one hand several studies did not find a harmful effect of moderate alcohol usage regarding either with peripheral vascular disease (Camargo et al. 1997; Ruitenberg et al. 2002) or COPD (Kaluza et al. 2019), high levels of intoxication, usually derived from the chronic excessive alcohol consumption, are associated with numerous ocular (Karimi et al. 2021) and vascular morbidities that may result in blindness or even death respectively (Piano, 2017).

5.4.3.3 Ocular spectrum diseases

This was the second most prevalent multimorbidity pattern in the male sample population with 18.7%. The title aims to reflect morbidities that involve vision impairment. Specifically, glaucoma is a group of progressive optic neuropathies characterised by the degeneration of retinal ganglion cells, that leads to visual field loss,

and has been identified as one of the leading causes of blindness (Tham et al. 2014). Blindness refers to severe visual impairment caused by various factors, including glaucoma and cancer (Bourne et al. 2013). Age seems to play a crucial role. In the present analyses, those in the older age group (67+ years) accounted for 73% of those with ocular spectrum multimorbidity, while for the younger age group (18-45 year) it was only 1.2%. An indication of an onset point is regarded to be the middle-age (46-66) where a large proportion of 25.8% of males in this age group found to have developed the specific multimorbidity pattern.

Several studies that examined ocular morbidities in middle and older age populations support this argument. For example, smoking has consistently been suggested as an independent modifiable risk factor for several eye diseases with dose-response effect (Cheng et al. 2000). Specifically, smoking has been found to increase the risk for glaucoma development and progression (Kang et al. 2004), vision loss (WHO, 2022), age-related macular degeneration (AMD) (Velilla et al. 2013) and uveal melanoma cancer (Smaldone et al. 2014). Additionally, studies that examined the relationship between alcohol consumption and glaucoma have yielded mixed results. A current meta-analysis identified a positive association between any use of alcohol and open-angle glaucoma, OAG (1.18; 95% confidence interval (OR= 1.02–1.36; CI 95%, p=0.03; I^2= 40.5%) but with low confidence of evidence (Stuart et al. 2022). Evidence on physical activity is limited but suggests that it may be an important underestimated modifiable risk factor for developing glaucoma (Olszewska et al. 2020), mainly due to neuroprotective effects of physical activity by improving ocular blood flow and reducing intraocular pressure (Ong et al., 2018). Finally, diets low in retinol equivalents (e.g., insufficient Vitamin) and vitamin B1, as well as high intake of magnesium, are associated with increased risk of developing open-angle glaucoma (Ramdas et al. 2012).

5.4.3.4 Neurovascular and gastro-renal

This pattern was observed in 9.1% of the sample's male population. The factor name aimed to acknowledge the interconnectedness of the included morbidities, and emphasise their shared etiological factors. Dementia and stroke are categorised as neurovascular conditions (Gorelick et al. 2011; Kalaria, 2016) while dyspepsia and CKD to metabolic disorders (Vanholder et al. 2005). There is evidence of a clinical association

between the two groups of the pattern that is undeniable (Kuma and Kato, 2022; Pendlebery et al. 2009) and that shows similar pathological mechanisms, such as chronic inflammation, between neurovascular and metabolic disorders (Zanoli et al. 2020). Age is also a crucial parameter for this group of neurovascular and gastro-renal morbidities. In the present analyses, the majority (82.1%) of those influenced by the specific pattern were from the older male group of (67+ years), while the younger group (18-45) accounted for just 0.9%. However, there is also compelling evidence of an important role for SNAP-multibehaviours as modifiable risk factors for the development of the morbidities including within this multimorbidity pattern. There is a clear indication that middle age group (46-66) mark the onset of SNAP-HRBs' deleterious effects, as is found since the 17% middle-aged males of the male group, were found to have developed the specific multimorbidity pattern.

Numerous studies have shown that SNAP-HRBs influence the development of these types of morbidity. Specifically, smoking is a well-known risk factor for dementia (Anstey et al., 2007), stroke (Shah and Cole, 2010) and chronic kidney disease (Orth et al. 1998) by producing neurodegeneration (Mhatre et al., 2008), vasular damage (Janina Markidan et al. 2019) and impaired renal function (Jha et al. 2013), respectively. Similarly excessive alcohol is associated with an elevated risk of dementia, affecting brain structure and function (Luchsinger et al. 2014; Mukamal et al. 2003). It also increases the risk of stroke, contributing to generation of ischemic events (Reynolds et al. 2003). A well-acknowledged consequence of prolonged alcohol misuse, is the development of chronic kidney disease (Lai et al. 2019).

Again, lack of physical activity is also associated with increased risk of dementia and impaired cognitive functioning (Sofi et al. 2011), and stroke due to its contribution to high hypertension that may increase cerebrovascular events (Lee et al. 2003). Finally, poor nutrition and high fat diets have been shown to contribute to cognitive decline, increasing the risk of dementia (Singh et al. 2014) and stroke, (He Feng et al. 2013), while high sodium diets increase the risk of chronic kidney disease (Barsotti et al. 1996).

5.4.4 Comparison with other studies

Direct comparison of the present study's patterns with those of other studies is challenging, mainly due to high heterogeneity between studies' designs (e.g., study's' population, included morbidities, data sources), and implementations (e.g., statistical analyses). The present study is among the few, like Prados-Torres et al. (2012), that have investigated multimorbidity patterns and not limiting to older adults in an effort to increase their clinical value. Most studies, (Abad-Díez et al. 2014; Foguet-Boreu et al. 2015; Wang et al. 2015) focused on older adult population, possibly overestimating morbidities correlations. Similar to most other studies, the present analyses focused on a finite number of morbidities (Cornell et al. 2009). However, while others studies used the ICD-10 to examine the disease categories (Foguet-Boreu et al. 2015; Schäfer et al. 2010), the present study used the list of 40 morbidities derived from Barnett et al. (2012) that were defined by Read codes in the clinical coding system used in UK general practices. Furthermore, in line with most studies, the present analyses examined multimorbidity patterns in both sexes. Few have conducted single sex studies (e.g., Jackson et al. (2016) examined multimorbidity patterns on elder women).

Data source is another field of heterogeneity. This study among others (Abad-Díez et al. 2014; Prados-Torres et al. 2012) used primary care EHRs as the main data source. Others focused on the general population (Foguet-Boreu et al. 2015), or specific samples (e.g., Cornell et al. (2009) focused on Veterans; Schäfer et al. (2010) focused on a statutory health insurance company; Jackson et al. (2016) use a sample of an Australian longitudinal study). Finally this study is among those (Jackson et al. 2016; Prados-Torres et al. 2012; Schäfer et al. 2010; Wang et al. 2015) that used EFA as their main analytical method, rather than cluster analyses (Cornell et al. 2009; Foguet-Boreu et al. 2015).

Despite heterogeneity in design, some of the identified patterns resemble some of those of previous studies. Specifically, the cardiometabolic-vascular (identified in both sexes) seems to be the most consistently observed and dominant pattern and as such, has important clinical value. Despite minor variabilities, it has been identified in the most of studies (Abad-Díez et al. 2014; Holden et al. 2011; Jackson et al. 2016; Kirchberger et al. 2012; Prados-Torres et al. 2012; Wang et al. 2015) that examined multimorbidity patterns. Prados-Torres et al. (2014) systematic review found the specific pattern to 10 out of the 14 studies they have examined. Respiratory patterns, as identified here, were

another match to patterns emerged in previous studies. Specifically two studies, Holden et al. (2011) and Jackson et al. (2016) also found a respiratory patterns in their populations. Lastly, Holden et al. (2011) gastrointestinal and cancer pattern is closely resembled the one reported in present study called genitourinary tract disorders and was identified in the sample's male population. Both patterns share gastrointestinal disorders and cancer. However, in the present study, prostate disorder is also included in the pattern, thereby influencing the pattern's name. Neither psychological nor mechanical-musculoskeletal patterns were identified in the present study, despite being suggested as frequently appearing ones by the systematic review of Prados-Torres et al. (2014).

5.4.5 Strengths and limitations of the study

The inclusion of large number of participants and morbidities strengthen the outcome of the certain study. This was augmented further with the usage of EHR that secured the extraction of high-quality data in relation to sample. Nevertheless, EFA itself seemed to be among the study's assets providing further rigour to study. Moreover, in contrast to cluster analysis, EFA seemed to serve better study's goal by allowing morbidities to interact with each other and permitting a single morbidity to exist in different patterns, something not permitted in cluster analysis, producing non-ecologically valid patterns (Schäfer et al. 2010).

EFA was also an efficient statistical method for tackling multimorbidity's complexity. Following the recommendations of Osborne et al. (2011), EFA revealed a concise picture of limited numbers of significantly stable and clinically value multimorbidity patterns, resistant to possible confounding influences of inaccuracies that may follow doctors' diagnoses or lifestyles recommendations. Moreover, the inclusion in analysis of only highly prevalent morbidities (>1%) is paired with the high rate of cumulative variance explained by extracted factors (56.69% for females and 61.75% for males). This is followed by an adequate goodness of fit regarding with the sampling accuracy (KMO measure 0.80 for females and 0.68 for males). Additionally, the inclusion to factors of only those morbidities with eigenvalues above 1%, and with factor scores' threshold of 0.30 (as the minimum acceptable value for a clinical and statistically significant

correlation between morbidities) provide further support to the above-mentioned argument.

The formation of factors that are easily interpretable is another added value of EFA, producing clinical useful results. It is notable that even when two morbidities formed a pattern (respiratory), this was based on Osborne et al. (2011) suggestion that a factor with only two morbidities can be accepted when the morbidities have high factor loadings and are conceptually related (as was this case with COPD and Bronchiectasis).

However, the present study also suffered some limitations. Firstly, while the number of morbidities in the present study was considerable, it may not have been exhaustive and could have missed important morbidities. Specifically, obesity was not included in the list provided by Barnett et al. (2012), thus it was not possible to identify it within the analyses of the present study. However, obesity has been consistently found to be associated with various patterns in previous studies, such as the musculoskeletal pattern (Cornell et al. 2009; Prados-Torres et al. 2012).

Second, there are limitations of the EHRs themselves and how morbidities or the lifestyle behaviour were recorded by doctors or GPs' personnel. It could be argued that due to a lack of rigorous unifying recording system for SNAP-HRBs, their vulnerability to over- or under- representation cannot be ignored. Furthermore, diagnoses of specific morbidities that usually play secondary roles may also be underreported in patients' EHRs, in comparison to primary conditions. This may come as result of mono-morbid healthcare system's treatment protocols that are primarily focused on more "serious" or "urgent" patient's morbidities that usually need periodic re-examinations.

Finally, researchers like Schäfer et al. (2010) argued that excluding people without multimorbidity from EFA analysis it could produce an overestimation of correlation between morbidities biasing correlation matrix. However, the counterarguments are also persuasive. For example, by studying the specific population it may provide a better understanding of the complex interplay between SNAP-HRBs and their associations with various morbidities. Eventually, this process may reveal a shared etiology since specific SNAP-HRBs share common underlying causes or mechanisms. By focusing on people with multimorbidity that have engaged with SNAP-HRBs, the emerging patterns may have reflected these shared etiological factors, uncovering novel association and

pathways that contribute to the development of multimorbidity patterns. Furthermore, identified multimorbidity patterns may be more relevant and generalisable to such high-risk populations, e.g., young adults who engage in multiple SNAP-HRBs.

5.4.6 Implication for future research and the healthcare system

The confirmed narrative of the present study signifies that SNAP-multibehaviours are key determinants of multimorbidity patterns is of clinical and academic-research value. The recognition of patterns (i.e., as cardiometabolic-vascular or respiratory), while possibly anticipated from existing literature, doesn't diminish the significance of current evidence regarding well-established associations between specific SNAP-HRBs (like smoking) and particular morbidities (such as COPD). Especially, when other emerging multimorbidity patterns, such as “respiratory and vision spectrum disorders”, challenges current understanding on how included morbidities may interconnected other than purely statistically. However, even for this pattern, Houben-Wilke et al. (2017) argued for an under investigate interconnection between morbidities, suggesting the need for more intense efforts on aetiological research of multimorbidity patterns and their association with multiple SNAP-HRBs.

Specifically, no research was found that examined the accumulated association of SNAP-multibehaviours on (multi)-morbidities included within the emerging patterns, except from some for respiratory conditions. This indicates an important gap in current knowledge to address. Multimorbidity-SNAP-multibehaviours have already been proposed, as it has been shown in Chapter 4, as a new multidisciplinary framework for future clinical practice and research.

Only one pattern is associated with the cardiometabolic-vascular cluster of morbidities, exhibiting noticeable sex differences in manifestation despite alignment with previous studies (Prados-Torres et al. 2012; Schäfer et al. 2010). This observation suggests the possible existence of different determinants or, where similarities exist, differences in the magnitude of the effect (Jackson et al. 2016).

Finally, the implication for the healthcare system is clear. There is a need to shift from single disease-based clinical practice guidelines to a more person-centred approach. An approach that will put the healing relationship between the healthcare provider and the

patients with multimorbidity at the centre and where multimorbidity and SNAP-multibehaviours at the heart of patient complexity inquiry.

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Having scrutinised the associative patterns emerging from the interrelationship between multimorbidity and multibehaviours, the project delves into more practical considerations concerning the healing relationship between healthcare providers and individuals with multimorbidity. This following chapter explores the combined impact that multimorbidity and multibehaviours may have on this relationship, leading to a shift in focus towards concepts such as the interpretive turn and postmodernism, alongside the contemporary definition of experiential multimorbidity proposed by Blarikom et al. (2023).

6. Examining healthcare relationships between healthcare providers and people with multimorbidity using Situational Analysis

6.1. Background

Multimorbidity, the situation where a person suffers from two or more chronic conditions, is now recognised as a prime public health concern, affecting 15.4 million adults in England, and accounts for about 32% of annual consultations in primary care (Bower et al. 2011) which is translated to 70% of national healthcare costs (Engamba et al. 2019). Progress in preventive and curative medicine, improvements in social life and modern 'westernised' unhealthy lifestyles, have all contributed to this situation of people living longer, but spending more years in ill-health (Sauvage & Ahluwalia, 2016; Loprinzi, 2015). These statistics are becoming even more alarming when taking into consideration two extra evidence, the social patterning associated with multimorbidity, and the increase expectancy in longevity achieved in recent years. For example, regarding the first, the well-known study of Barnett et al. (2012) has shown that the onset of multimorbidity may begin as early as 10-15 years earlier for those living in a deprived area compared to those of higher social strata. For the latter current estimations by WHO show that the average longevity after 60 years of age is approximately 22 years (Miyata et al. 2022). The implication is clear: people may live longer, but with the majority of those additional live years will be in poor health (Sauvage & Ahluwalia 2016). A projected estimation indicates that approximately 17% of the UK population will suffer from four or more chronic conditions by 2035, nearly doubling the current prevalence rate of 9.8% (Pearson-Stuttard et al., 2019).

However, a misconception that diminishes the seriousness of multimorbidity as a public health concern is that it has typically been treated (theoretically and clinically) as a geriatric issue (Whitty et al. 2020). While it may be true that the prevalence of multimorbidity rises with age, the numbers of those suffering from multiple conditions are from working age and under 65 years old (Barnett et al. 2012). This means that a substantial population of young and middle-aged adults will demand long term care and support by healthcare system's services (de Carvalho et al. 2019).

Among others, a parameter often overshadowed by this misconception, is the impact of the prolonged exposure to various modern unhealthy lifestyles on the increased incidence rates of multimorbidity (Alamian & Paradis, 2009). Indicatively, while the significance of individual SNAP-HRBs in the development of chronic conditions has long been recognised in the scientific community, leading formulation of specific clinical guidelines for managing single chronic conditions (NICE, 2016), only recently attention has been directed towards the interrelation between multimorbidity and multiple behaviours (Violan et al., 2014). This is, despite acknowledgment that health risk behaviours, like SNAP-HRBs, are the only modifiable parameter (Prochaska, 2008) among the other known contributors to multimorbidity (e.g., age or socioeconomic circumstance) (Loprinzi, 2015). For example, 30 years of epidemiological data from several European countries have shown that promoting healthier lifestyles within the healthcare system prevents and delays mortality and/or morbidity in numerous diseases (NICE, WHO, 2010).

Additionally, as discussed on Chapters 3 & 4, several studies provide additional evidence supporting this assumption (Schäfer et al. 2019; Zacarias-Pons et al. 2021; Jackson et al. 2016). Specifically, it has been shown that SNAP-HRBs are eligible precursors of multimorbidity (Afshar et al., 2015), having a positive dose-response association between the number of SNAP-HRBs and multimorbidity risk (Loprinzi, 2015; Agrawal et al., 2016; Dhalwani et al., 2017) that is stronger than those identified by single health risk behaviours (Fortin et al., 2014; Katikireddi et al., 2017). This evidence directly implies the need for a shift in policy and healthcare provision toward an integrated preventative and curative medicine framework (Prochaska, 2008) that will eventually lead to a unified multimorbidity-multibehaviours clinical research and practice (Loprinzi, 2015).

Therefore, it seems contradictory that despite the prevalence of multimorbidity, its strong association with lifestyle choices and its increasingly common occurrence in healthcare settings, there is no clear evidence-based clinical recommendations that reflect these medical and behavioural complexities, independently or combined (Engamba et al. 2019; Bower et al. 2011). In turn, it is no surprise that this perplexing situation related with multimorbidity-multibehaviours interrelationship poses a considerable challenge to mono-morbid healthcare systems worldwide (Barnett et al., 2012; Prados-Torres et al., 2014).

Unfortunately, reductionist thinking, and a single disease-based approach still dominate curative medicine policy and protocols (Damarell et al. 2020), jeopardising the optimal care for people with multimorbidity (Smith et al. 2012; Kamerow, 2012). For example, the effectiveness of the successful endeavour of the Chronic Care Model (Bower et al. 2011) that is applied to most healthcare systems and focuses on evidenced-based guidelines for better managing the care of patients with a single chronic condition is questionable when applied to people with multimorbidity (Salisbury et al. 2018; Sathanapally et al., 2020). Particularly, the National Institute for Health and Care Excellence (NICE, 2016) requests clinicians' to be cautious when they implement these single disease-based guidelines to people with multimorbidity due to the considerable risk of these guidelines contradicting each other in various health-related issues e.g., medication (McKenzie et al., 2018). Encouragingly, scholars have started to request the development of guidelines for multimorbidity (Damarell et al. 2020) in the form of generic principles that shift the guidelines focus from disease-specific to person-centred care, including possible lifestyle factors of the patient (McKenzie et al. 2018). As Hughes et al. (2013) stated, what is needed are "Guidelines for people, not for diseases".

Another example of how suboptimal care may emerge within the healthcare system is the overreliance on referral and signposting policies without further collaboration between healthcare professionals (Smith et al. 2012). The aftermath of this poor communication is directly related to the fragmented and uncoordinated healthcare delivery (Stumm et al. 2019), as projected via multiple appointments with various healthcare professionals and services across different parts of the healthcare system.

Such systemic failures (NHS, 2018) jeopardise patient safety (Mercer et al. 2016), especially when a usual multimorbidity treatment is accompanied by complex pharmaceutical regimens that are rarely without contradiction (Damarell et al. 2020) or can lead to low treatment adherence (Turabian, 2019). Consequently, higher rates of hospitalisations (Kamerow, 2012) (re)admissions to acute health services (Turabian, 2019) and increased vulnerability to acute health threats (Mercer et al. 2016) seem "logical" consequences of uncontrollable multimorbidity at a systemic level. However, the consequences of multimorbidity are not solely apparent at population level. Suboptimal care for multimorbidity patients may hasten a deterioration of their functional, physical, and mental health status, abandonment of their self-management

procedures and their effort to apply necessary lifestyle change(s), high risk to adverse drug-related events due to their polypharmacy, and poor social life. All well-acknowledged situations in literature are attached to personal burden (Smith et al., 2012; Salisbury et al. 2018).

To address these issues, it has been widely agreed that the aim of healthcare systems must be to upgrade some of the Chronic Care Model's features, focusing more intensely on providing person-centred care (Salisbury et al. 2018). In short, parallel with the usual Chronic Care Model's required changes, there are demands toward a more proactive, integrated and coordinated provision of healthcare (Sturmberg & Martin, 2013; Coulter et al., 2013). Five main areas have generally been agreed to accompany the suggested patient-centred model: Exploring the subjective experience and anticipations of disease and illness, comprehensive understanding of the multimorbidity patient, consensus between healthcare professional and multimorbidity patient regarding multimorbidity management, health promotion, and establishment of good doctor-patient relationship (Little et al. 2001; Kamerow, 2012; Moody et al. 2022).

Consistent attention to these areas supports the routine, thorough examination of multimorbidity patients' unique situations and proper customisation of their treatment plan to align with preferences and current circumstances. This will further permit a better examination of treatment benefits and risks, helping to minimise treatment burden either regarding inappropriate polypharmacy or integrated care and better organisation of the services delivered by a multidisciplinary team (Salisbury et al. 2018).

To date, randomised control trials (RCT) of interventions that applied a person-centred model of care have produced but mixed results for hard clinical outcomes (Smith et al. 2021), prompting Cochrane collaboration to advocate a shift in research interest away from morbidities per se, towards outcomes relevant across range conditions (e.g., quality of life). However, in pursuit of this goal, Salisbury et al. (2018) found that their well-known 3D intervention failed to demonstrate any improvement in patient’s quality of life. Possible explanations include the limited duration of follow-up of six months (Salisbury et al. 2018) or the unsuitability of RCT to capture the complexity of care that attached with multimorbidity patients. For example, multimorbidity patients are often excluded from participating at RCT studies because of their multiple conditions (Smith et al. 2012). Variability in clinical care processes and decision-making can arise from the

complexity of conditions extending beyond just multimorbidity. This complexity often involves factors such as socioeconomic status, cultural background, and behavioural patterns, leading to unpredictability in healthcare delivery (Grant et al., 2011; Webster et al., 2019).

For the current study, complexity refers to the medical and/or behavioural complexities (independently or combined) with the behavioural ones to have an extra characteristic, the one of complexity moderator (Ben-Menahem et al. 2021). Thus, the research question that this chapter aims to examine is how complex interrelationships between multimorbidity and multibehaviours 'construe' the healthcare provider-recipient relationship and are 'constructed by' it. Furthermore, particular gravity was given to the overshadowed voices of people with multimorbidity, especially if/when these are challenging the normativity of currently applied treatment policies. To this aim, the establishment of a "therapeutic alliance" between multimorbidity patients and their health care professionals has been suggested as a key factor and a powerful tool for overcoming these complexities, especially in the absence of evidence-based guidelines (Turabian, 2019) and this will be the guiding metaphor for this chapter.

6.2 Methods

6.2.1 Study design

A qualitative study design was chosen as the most appropriate to examine the experiences of those who participate within healthcare relationship (healthcare providers and people with multimorbidity) regarding how multimorbidity (medical complexities) and multibehaviours (behavioural complexities) can complicate the care treatment process.

Abductive reasoning from the literature indicates that the complexities that accompany multimorbidity and multibehaviours phenomena and projected in partners of the healing relationship in various forms, are obscured by powerful existing constructs. These include medicalisation that perpetuates the mono-morbid healthcare system provoking power imbalances, challenges, and contradictions between key social players while jeopardising the safety of people with multimorbidity as a result of polypharmacy. Thus, the main priority for this project was to use a research method able to

acknowledge and fully grasp and address all nuances and complexities experienced by healthcare providers and people with multimorbidity in real-world healthcare settings without oversimplifying the information to make the results easier to digest.

6.2.2 Situational Analysis overview

Situational Analysis was designed to unpack nuanced complexities inherent in real life situations, like those of the present project (Clarke, 2005), where linear-based methodologies of cause and effect, as those implemented so far within this PhD thesis, seem ineffective and inefficient (Rutter et al., 2017).

Acknowledging the importance of complexity itself as the subject of investigation means that claims of the universality of the situation of inquiry, mainly due to positionalities, contradictions, tenuousness, and numerous other internal differences seem naïve or, according to post-modernist view, susceptible to perpetuating the power of knowledge to those mostly producing it and usually in positions of power, authority, or legitimacy to exert it (Clarke, 2005). By "enforcing" the universality construct, theories and methodological approaches based on modernism eliminate any voices that challenge commonalities or exist at the edges of the scientifically constructed "normal curve", characterising them as "noise" or "outliers" and treating them as something of no importance (Clarke et al. 2018).

The adoption of Situational Analysis as the project's methodology represents the exact opposite of this modernistic thinking. In short, when implementing Situational Analysis, nothing is taken for granted, especially on issues that seem 'normal' within the situation and, therefore, may have been internalised and thus become invisible (Clarke et al. 2018). Minor discourses or issues are given equal consideration as those that appear to be major or more prominent because they may be indicative of power imbalances. Similarly, deviations from the norm are not treated as exceptions but as the boundaries of the situation under investigation (Whisker, 2018). In this sense, Situational Analysis manages "to replace metaphors of normal curves and normativity with relational metaphors of ecology and cartography" (Clarke et al. 2018 p.52), embracing the situational differences and positionalities.

This was the initial endeavour that gave the impetus to Situational Analysis before it became a distinct and independent post-modern methodology (Whisker, 2018). This

marked a departure from its precursor, Grounded Theory, moving away from the creation of theoretically generalisable grand narratives concerning the underlying social processes of the phenomenon, (Wulff, 2008). Instead, Situational Analysis suggested an alternative grounded theorising of a situation-centred methodology able to provide a "thick analysis" of all human and non-human elements that are embedded and interrelated and negotiated within the complexities of social situations via a map-making conceptual framework (Martin et al. 2016). Such "thick analysis, goes beyond the "knowing subject" while furthermore it acknowledges "that things could be otherwise" (Clarke et al. 2018). The primary objective of the current project was to fully elucidate the intricate social complexities of the situation and generate reflexive and insightful theoretical assumptions regarding the emergence, interaction, and influence of medical (multimorbidity) and behavioural (multibehaviours) complexities on the relationships between healthcare providers and multimorbidity patients, whether collectively or independently. Practically, this means that Situational Analysis was implemented as a three-step iterative methodology, where each phase informs and is informed by the next/previous one. There are no fixed boundaries between the three analytical stages. Data collection/analysis of each phase depends on the findings of the previous one, but there is a constant recursive analytical loop (where earlier stages can be amended based on findings from subsequent stages) until saturation of evidence is achieved. Constant memoing (Bircks et al. 2008) and reading and re-reading of the data assisted the researcher in overcoming of what is known from the qualitative literature of research (Clarke et al. 2018).

The final outcome is three series of cartographic conceptual maps (situational maps, social worlds/arena maps, positional maps) (Clarke, 2005). These detail the picture of the non-linear interlinkage and complex structures of multimorbidity – multibehaviours with each other and other sources of the complexity of situation under inquiry; namely "**healthcare provision for people with multimorbidity in the Staffordshire, England**". The three Situational Analysis phases comprised:

- Situational maps that further comprised by messy, ordered, and relational maps, where all important human, nonhuman, elements of the situation under investigation were examined.

- Social worlds/arenas maps, where all collective actors (humans) and actants (non-humans) were analysed in relation to the arena in which they were engaged and negotiated the related to situation discourses.
- Positional maps illustrated all positions (taken and not taken) that emerged from data around key discourses or issues of concern or major controversies that accompanied the situation under investigation.

Finally, another major advantage of Situational Analysis' cartographic infrastructure is flexibility to be applicable in various forms of project designs, whether single (mono method) or mixed methods (e.g., integrating the analysis from more than one method of analysis). In this case, due to the limited time and resources, Situational Analysis was followed as a mono-method project that gathered information almost exclusively via in-depth interviews and one focus group. Further examination of extant narratives via case studies, articles, websites, and reports (Appendix 18) was considered appropriate to verify the emergent discourses within the situation of inquiry.

Ethics for the present study was approved by Staffordshire University's ethics committee (09/11/2022; Appendix 19), while informed consent was obtained prior to data collection (Appendix 20).

6.2.2 Participants

A purposive sample was recruited comprised of health professionals and member of the public with multimorbidity:

- Eight healthcare providers (e.g., General and Specialist practitioners, Public health doctors, and Nurses) who had three years or more experience in delivering health care
- 10 members of the public who acknowledged themselves as having multimorbidity (two or more chronic conditions) that at the time of their diagnoses engaged in two or more SNAP-HRBs or needed to apply a health behavioural change to at least two of those.

Each group was recruited independently (as below), while theoretical sampling was implemented as a key process within Situational Analysis in pursuit of situatedness and variation (Clarke et al. 2018).

6.2.3 Recruitment

There was a combination of opportunistic and snowball sampling as participants in either group shared similar criteria and could be reached via existing contacts and networks (Mack et al. 2005). For healthcare professionals, an email was sent on behalf of the researcher to the "Friends of CHAD" network (Appendix 21), comprising a list of individuals who have registered their interest with the Centre for Health and Development (with which the researcher is affiliated). This includes various professionals, including those working in health care. To those who responded, a Participant Information Sheet was sent (Appendix 22), allowing potential participants to familiarise themselves with the study's purpose, eligibility requirements and withdrawal rights. If an individual expressed an interest in participating, a consent form (was sent via email. Once participants expressed their willingness to proceed, they were asked to complete and return the consent form and a mutually convenient time for the interview was agreed.

For members of the public, an email was sent by the researcher to colleagues who are known to the Centre for Health and Development (CHAD) who work with communities and public groups (e.g., third-sector organisations) and with whom CHAD has long-term collaborations (Appendix 23a). Those contacts, in their turn, sent an email (Appendix 23b) to those members of the public known to them (who might be eligible to participate) asking to respond directly to a researcher in case of interest. Those who responded received the Participant Information Sheet (Appendix 24) to familiarise themselves with the study's purpose, eligibility requirements and withdrawal rights. If an individual showed an interest in participating, a consent form was sent via email and a time arrange for researcher to contact them via telephone to check eligibility. During this call, participants had the opportunity to ask questions and further discuss the research. Once participants were willing to proceed, they were asked to complete and return the consent form and a mutually convenient time for the interview was agreed.

6.2.4 Interview procedures

All interviews took place either online (MS Teams) or via telephone. They were semi-structured to allow a more open discussion. A semi-structured interview uses pre-existed topic guide while allowing the flexibility to modify the questions based on the conversation's flow, ask additional questions if appropriate for delving deeper into the interviewee's experience (Robson & Mc Cartan, 2016). The interview topic guides were developed (Appendices 25 and 26) in partnership with the supervisory team. On completion of the interview, a debrief (Appendix 27) was given to each participant. During this process, appropriate information about the nature of the study, the purpose of research, etc., was given, while the researcher answered any questions that had arisen from any participant regarding the study, its participation, or the Interview process itself. Interviews were audio-recorded and transcribed verbatim (by PhD researcher and a professional transcriber - an external partner of CHAD) for analysis. Participants who were members of the public were offered a £30 retail voucher in appreciation of their time.

6.2.5 Focus group procedures

As part of the theoretical sampling process, it was considered necessary to design a focus group with people with multimorbidity. The decision to implement a focus group rather than individual interviews was based participant preference. Four of the 10 public participants expressed a preference of a focus group, which was advantageous in fostering interaction and discussion among participants (Wong, 2008).

The duration of the focus group (four members) was approximately 2.5 hours, with one moderator, (PhD researcher). Predetermined, open-ended questions (Appendix 28) that followed the same topic guide as interviews were used to elicit feedback on how medical complexities (multimorbidity) and behavioural complexities (multibehaviours) impact if at all, their treatment process, and their healing relationships with their healthcare providers. At the beginning of each group, the PhD researcher introduced himself to the participants, letting them do the same with each other, and informed them that in case they didn’t want to reveal their identity, they could use pseudonyms. At the end of the focus group, participants were debriefed in a similar fashion as those participants who participated in interviews. Similarly, the focus group was audio-recorded and transcribed

verbatim (by PhD researcher and a professional transcriber - an external partner of CHAD) for analysis in the same way as interviews. Again, since participants of the focus group were solely members of the public a £30 retail voucher was offered in appreciation of their time.

6.2.6 Data analysis

The analysis of interviews and focus group transcripts employed the phenomenography methodology. Clarke et al. suggested phenomenography over phenomenology for analyzing interviews due to its emphasis on identifying variations in how individuals experience a particular phenomenon, rather than focusing solely on shared meanings, for which phenomenology would have been more suitable. However, in the present study, the applied approach emphasised methodological principles of phenomenography over strict adherence to its theoretical framework. This was due to our pragmatic goal of identifying and comprehending the diverse perspectives of various groups (healthcare providers and/or people with multimorbidity), thereby supporting the identification of key variations in positions taken—and not taken—regarding the investigated situation.

Phenomenography researchers, furthermore, have argued that while individuals may interpret a phenomenon in countless ways, within the process of understanding the meaning, only a limited range of interpretations will persist. Consequently, the ultimate result will be the "categories of description" — labels derived from the induction process of analysis that most accurately capture the diverse ways participants understand a phenomenon at the collective level. (Larsson & Holmstrom, 2007).

Extensive reading was conducted for familiarisation with data before data were coded and initial themes generated. Memoing constantly supported all this process. The analysis examined the collected interviews individually and collectively, generating categories of description that encapsulate a manageable number of comprehensive meanings of healthcare providers and people with multimorbidity experiences regarding the healing relationship process (outcome space). Themes were then developed and reviewed to ensure they were data-driven. The analysis involves repeatedly reviewing the developing interpretations in relation to the transcript data during various analytical stages. However, the actual analysis commenced only after all interview transcripts were

prepared for comprehensive reading by the researcher. The analytical approach focused on analysing large chunks of interview transcripts related to a particular issue. The decision to focus on large segments was based on the suggestion that such an approach aids researchers in accurately interpreting the underlying meanings behind the participants' words (Akerlind et al. 2005). Saturation of the emerging themes is achieved by establishing a 'dialectical' connection between the 'content of meaning' (descriptive categories) and the structural meaning (the hierarchical organization of the outcome space among categories) (Akerlind et al. 2005). In the end, this process not only allowed the identification of the variation (between and within the health professionals and members of the public groups) regarding the conception of the phenomenon being investigated but also fed the issues emerge via social worlds/arena and positional maps.

Data coding was conducted by the PhD researcher (KS). Indicatively the coding procedure follows a specific pattern. This was then refined, defined, and verified by the researcher's supervisory team (Appendix 29). To be more specific, a unique coding system was used. Each participant receives a specific code that is known only to researcher (KS) indicating its place within the interview order. This code was further accompanied a number indicating to researcher where within the specific interview the specific coding appears. As such, the P1, 11, coding is simply referred to the eleventh comment of the first interviewed participant.

6.3 Implementation of Situational Analysis

6.3.1 Situational Mapping and Analysis

During this phase of the project, which centres on constructing and analysing a series of cartographic conceptual maps, it's essential to keep two key points in mind all the time. Firstly, on a theoretical level, it is important to remember that each conceptual map presented, serves the overarching goal of enhancing understanding of the situation of inquiry, or as Clarke et al. (2018, p.18) put it “things could always be otherwise”. These maps above all are units of analysis, with the analysis process thought to be integral part of their construction. Secondly, on a practical level, the analysis of the above-mentioned maps is an iterative process that involves continual updates throughout the project, with newly gathered data informing subsequent steps. This iterative approach mirrors

“theoretical sampling in action” Clarke et al. (2018, p.140) where each stage builds upon and refines insights from previous ones.

6.3.2 Situational maps

This stage was entirely bibliographic and involved the collection and analysis of material related to the situation of inquiry to identify all of the elements (humans and non-humans) that are of particular importance to the investigated situation and which elements may make a notable difference with their inclusion (Clarke et al. 2018).

Embracing the ideas that emerged from philosopher Derrida regarding the need for equality in the treatment of verbal and written words by the scientific community, Situational Analysis recommends that all sources of written and spoken information can equally contribute to a better understanding of the situation under investigation. Going a step further, Situational Analysis claims that everything that previously could be regarded as the surrounding context of an inquired phenomenon can now be regarded as a “constituent” part of the situation itself (Clarke et al. 2018).

Thus, a series of articles, project reports, case studies, and websites were examined by the present researcher such that important extant narrative(s) of the situation were extracted and to support continuous development of all types of situational maps (abstract/messy, ordered and relational).

According to Situational Analysis, the first action accounts for the creation of the abstract/messy maps and the depiction of all these factors (humans, non-humans, discourses, symbols) able to contribute analytically to comprise the situation under investigation (Appendix 30) as broadly comprehended. The importance of following this inclusive approach is related to the analytic power of abstract/messy maps to identify issues (e.g., discourses) that, until the moment of specific inquiry, were “taken for granted”, escaping any critical consideration. One such issue that was of immediate interest in the present study was interchangeable use of comorbidity and multimorbidity terminologies in health-related literature and the practical consequences of health delivery practices driven by the specific linguistic construct. For example, how health professionals' accounts that inclined traditionally more toward the comorbidity term

appeared related to actions more closely aligned with the biomedical rather than a biopsychosocial model of care.

After a series of abstract/messy maps and when a steady version was developed, all identified elements were arranged within the specific categories of the ordered map (Appendix 31). This specific map's critical analytical significance and purpose is to help the PhD researcher to fill possible gaps using a familiarised version of the analysis (Clarke et al. 2018). With the completion of this intermediate step, the development of relational maps commenced.

Relational maps emerged from depicting the interrelations between the included elements. To fully grasp the situation of inquiry, several relational maps were generated. For their creation, the current researcher used an electronic version of developing relational maps rather than the traditional hand-made ones, targeting their better presentation and readability (Appendix 32). Thus, the strength of association between elements in this spiral formation relational maps is indicated by the closest position of the connected element to the central element under investigation.

This shift of analytical focus away from the elements per se toward the significance of their interrelationships indicates the usage of post-structural ideas within Situational Analysis to deconstruct various power dynamics of multiple emerging meanings underlying the numerous heterogeneous interconnections (Eunicke et al. 2023). This analytical process that accompanies the construction of numerous relational maps allows the researcher to rethink the situation of inquiry more holistically, deciding which relations are more important to pursue later on, in interviews (“theoretical sampling in action”) (Clarke et al. 2018, p.140). Specifically, the symbolic interconnection of the notion of “time” either referring to the amount of time people with multimorbidity spend on their self-management or to the consultation time with various healthcare providers at different sites of a healthcare system (e.g. Primary versus Secondary care consultation time), is such an example that has been further investigated later on in this project.

6.3.3 Social worlds/arenas maps

Creating a social worlds/arenas map was the milestone of this analytical stage that was mainly based on the information gathered through interviews and supported by selective bibliographic research (Appendix 18) and memoing. However, the documents were chosen as a convenience sample instead of through a systematic review, mainly due to time restrictions posed by the PhD requirements. This selection was mainly based on their relevance to the research questions being explored, their availability to be retrieved, and their ability to provide diverse perspectives on the situation being investigated. The social worlds/arenas map aims to illustrate the collective action of all actors-humans/actants-nonhumans within the situation of inquiry. By the notion of collectivities, Situational Analysis emphasises the perspective, discourses and commitments shared by the agents of a particular social world as those reflected via the implementation of their primary action(s) and/or technologies they possess in their pursuit of better control of a situation of inquiry, otherwise called arena (Clarke et al. 2018). For the present project, the "**healthcare provision of people with multimorbidity in the Staffordshire, England**" was set as the arena where numerous small and large social worlds, some central and others peripheral, operate, contrast, cooperate, collaborate, and/or negotiate with each other. According to Situational Analysis, every actor/actant has the potential to serve as an ambassador of a particular social world, with their actions possessing the analytical power to decode its intricacies. In this sense, the implementation of Situational Analysis methodology via the in-depth interviews with a heterogeneous group of participants active in various social worlds and specialties of healthcare (e.g., nurses, general practitioners, hospital specialist and community specialists) and people with multimorbidity, was helped to reveal the nuances and dynamics of the situation. In this sense, the analytical significance of this 'x-ray' process regarding the ecological complexity of the arena is to improve our understanding of what Clarke called the "social" or: '*the relational ecological form of organisational analysis dealing with how meaning making, and commitments are organised and reorganised again and again over time*' (Clarke et al. 2018, p.150). This is often omitted from individualistic qualitative inquiry.

Following Situational Analysis instructions, the project's social worlds were aligned to express either their collaborative action (with some form of proximity to each other) or their antagonistic relationship (positioned in opposite directions). The degree of intersection between them as well as with the arena of interest itself, indicated their interventional exchange. Finally, all social worlds have been presented in porous circles, indicating their intersectional nature (Figure 7).

The NHS (central yellow circle) is the primarily responsible social world for the provision of healthcare support services for people with Multimorbidity in England. This effort is further supported locally via the public health services that fall under the remit of Local Authorities (upper yellow circle). Two critical segments, Primary and Secondary care social worlds (blue circles), comprise the NHS, anticipating that their collaboration 'secures' its goal for comprehensive and the best possible provision of healthcare services from the "cradle to the grave" for all eligible population in England. This effort has been supported, when requested, by Community services that have been presented in this social worlds/arenas map as an independent social world that bilaterally intersects both the mainstream healthcare worlds of Primary and Secondary care.

The size and positioning of each one of the social worlds defines the magnitude of their involvement and the current level of power they exert in the situation, as well as in comparison to each other. This was recorded by interviews and further supported by bibliographic research about the number of activities they are engaged and the possession of specific technologies (Clarke et al. 2018). At the same time, their specific positioning indicates the existence and the extent (if at all) of collaboration between them based on the premises of the person-centred care model.

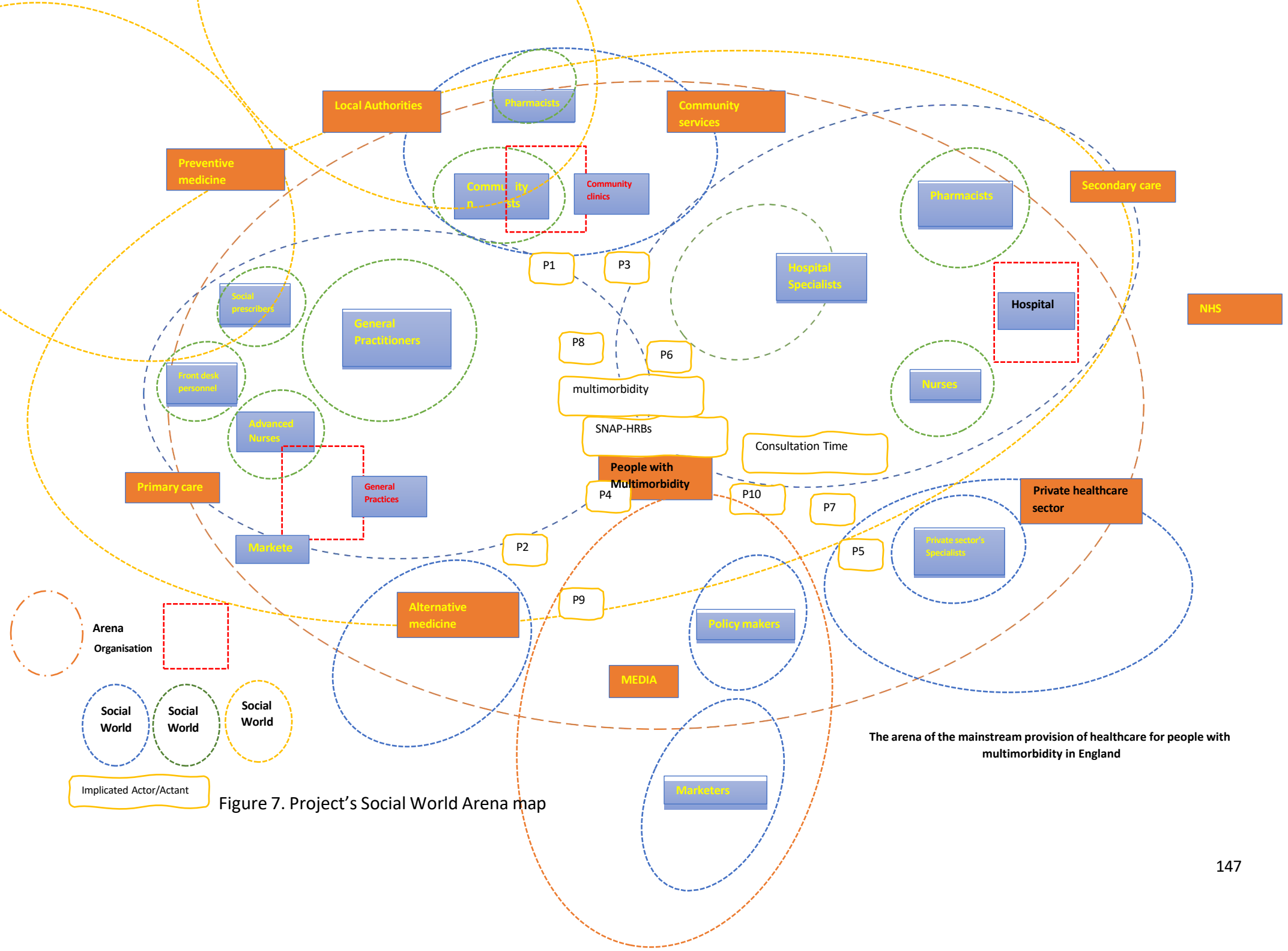

Figure 7. Project's Social World Arena map

The arena of the mainstream provision of healthcare for people with multimorbidity in England

The positioning of the above social worlds indicates the shortage of evidence of standardised provision of integrated care as, at least theoretically, someone would expect. Rather, fragmented and uncoordinated healthcare examples reflected a lack of central coordination via the Primary care social world actions, and issues with medication management coordination between secondary care specialists and pharmacists were apparent. Furthermore, the only service named as the officially responsible for the continuity of care for people with multimorbidity regarded the Advanced Nurse's annual check appointments within the Primary care clinics. In short, referral and signposting policies seem the only inter-sectoral link, but without further coordination and collaboration, it seems unlikely to meet the complex needs of multimorbidity-multibehaviours patients. The visual depiction of opposing Primary and Secondary care social worlds on the project's social worlds/arena map highlights this fragmentation of healthcare provision for people with multimorbidity identified through in-depth interviews. The theoretical basis for this positioning was based on Situational Analysis assumption that each segment indicates the internal differences within the social world (in this case the NHS social world), while the dynamics between them create tensions and debates, prioritising their own specific commitments and agendas.

Within person-centred literature concerning multimorbidity, Primary care is presented as the cornerstone of the healthcare system, able to offer holistic care to individuals with multiple health conditions. However, the present investigation in real-world settings paints a different picture. While Primary care has the opportunity for a comprehensive assessment leading to a personalised care plan, incorporating individual needs and priorities, and ensuring its effective implementation through regular monitoring, this ideal is seldom realised. Consequently, individuals with multimorbidity often resort to Secondary care, and if financially feasible, seek specialised care from private sector, albeit primarily focused on addressing a single primary condition. This discrepancy is evident in the magnitude of each social world mentioned above. A closer examination reveals that both Primary and Secondary care are significantly affected by the complex interplay of multimorbidity and multibehaviour phenomena.

Furthermore, the concept of segmentation elucidates the internal power dynamics within a social world, where individuals occupying central roles (entrepreneurs) influence the direction of the social world's actions, while those in peripheral roles (mavericks)

contribute to defining its boundaries through their participation. For instance, within the NHS social world encompassing Primary and Secondary care, the 'elite' group of doctors, including general practitioners and specialists, assumes the role of entrepreneurs. They shape and are shaped by the pervasive notion of medicalisation , which is employed to address the multifaceted needs of those with multimorbidity

At this point, the sensitising idea of “gaze”, developed by the French philosopher Foucault and analytically acknowledged recently by Clarke et al. (2018), is of crucial importance. “Gaze” regards a better understanding of the perspective of those in power and authority to impose control and homogenise what is considered necessary to a particular situation, suppressing, marginalising, and obscuring any alternative viewpoints. By those in power, Foucault usually meant the official institutions like medicine or government and their communication channels (e.g., health policies of deliverance of care) to promote their shape-making powerful discourses. In the present analysis, several gazes that have been identified and served meticulously by the entrepreneurs of the NHS social world are the healthcare professional’s medicalised approaches, the mono-morbid healthcare system, NICE guidelines, and/or the Quality and Outcomes Framework of healthcare services.

Enthusiast of post structuralism, Clarke (2005), developed the idea of implicant actor/actants, as an alternative pillar to the notion of “gaze”. This further ensures the examination and analysis of discriminant relationships and power imbalances within the social worlds/arena map. The central idea of this pillar is to make visible what is hidden, and to give voice to what is silenced (Ássimos & Pinto 2022). According to Clarke (2011), articulating the silenced data is what makes us ethically accountable researchers. Thus, having previously discussed the powerful actors, it is time to reveal those silenced. People with multimorbidity are presented in that form within the social worlds/arena map; not as collective actors of an independent social world but as implicated ones, despite being present, their voices are ignored by those with the power to decide (healthcare providers, policy makers etc.). This perpetuates the main narrative of medicalised healthcare focused on ‘curing’ the diseases rather ‘caring’ for the patients (Sauvage & Ahluwalia, 2016). Thus, different medical paradigms, depicted here as distinct social worlds, constructed different versions of caring and distinct types of patients, neglecting people’s with multimorbidity unique perspective and their complex health related experiences, in favour of advancing their own discursive constructions.

The positioning of individuals with multimorbidity across various social worlds, spanning from the peripheries of Alternative medicine to the Private sector and the mainstream NHS healthcare system, signifies their persistent endeavour: to voice their concerns, alongside their deep-seated frustration and sense of alienation stemming from the systemic failure to recognise their personhood beyond their multiple morbidities (Hamiduzzaman et al. 2022). This is the main reason for setting the majority of social world in an antagonistic and opposing placement to one another.

All the above were reflected within the in-depth interviews revealing contrasting findings about the treatment for people with multimorbidity. Findings showed a preference for episodic rather continuity of care, recommendations based on single-disease guidelines that overlook the personal history of people with multimorbidity. Within this, there was apparent variability in the applied assessment models, ranging from the simplistic assessment and advice to more advanced approaches such as motivational interviewing, and diverse consultation models (from the sequential decision model to more intense one of five Ps model).

Besides implicant actors, the present research highlighted several implicant actants, nonhuman entities that were discursively present, but obscured or manipulated by the dominance of medicalised care. Indicatively, during interviews, healthcare providers consistently used the term ‘comorbidity’ instead ‘multimorbidity’ regardless of medical background (and being asked questions about multimorbidity).

The implication of this symbolic interaction underscores the profound internalisation of the medicalisation paradigm among the key social actors. It reveals a gap between the theoretical assumptions toward person-centred care and practice. The emergence of the multimorbidity construct highlights the failure of the comorbidity terminology to address the holistic needs of individuals, perpetuating a single-disease mentality. It reinforces the medicalisation of care by prioritising dominant diseases over comprehensive patient-centred approaches." As McKenzie et al. (2018, p.8) put it “clinicians need to find ways to treat people not the diseases”.

A crucial component for this to be achieved, is the inclusion of the differential diagnosis process within a person-centred approach. Practically, this means the establishment of trusted relationships between the healthcare provider and the people with multimorbidity based on the mutual exchange of their expertise (medical knowledge and

lived experience) and the indexing of multimorbidity patients' personal history to diagnostic procedures. This is based on the facts regarding with the heterogeneity of the treatment outcome between people with multimorbidity (Weis. et al. 2014) even if they have received the same diagnosis (Levenstein et al. 1986). This requires a departure from one-size-fits-all policies and models, towards more person-centred ones, such as consultation techniques of Motivational Interviewing (McKenzie et al., 2018).

Motivational Interviewing serves as a person-centred technique focused on behavioural change, which is critical for effective management of multimorbidity. This narrative was widely embraced by all project participants and verified discursively in the multimorbidity management literature (McKenzie et al 2018). However, in real-world settings, the health risk behaviour change construct was identified as another implicant actant and illustrated as such within the specific social world/arena map. This decision was informed by the interview evidence demonstrating a lack of any standardised procedures among mainstream healthcare providers for assessing or intervening in health risk behaviours. For example, while assessing health risk behaviours was a standard procedure in secondary care, it was not in primary care unless a direct link to the presented morbidity was established. Even then, people with multimorbidity had to wait until follow-up appointments for a comprehensive health risk behaviour assessment. Furthermore, interventions for health risk behaviour were not consistently tailored but left to the discretion of healthcare providers. This essentially positioned healthcare as a normative authority, determining which multimorbidity patients would receive a health risk behaviour intervention for health risk behaviours (Agborsangaya et al. 2012). Health risk behaviours and associated techniques (e.g. Motivational interviewing) were standardised components primarily within the social world of community services, the 'mavericks' in healthcare delivery. However, only a restricted number of people with multimorbidity, typically through General practitioner referral, could access and benefit from these interventions.

A crucial parameter in adopting the person-centred approach and accompanying techniques is the amount of time required to consult with multimorbidity patients. The significance of time was acknowledged by all participants and particularly from people with multimorbidity. However, time and its symbolic interaction, serve as another implicant actant within the arena of healthcare provision to people with multimorbidity.

This is evident from the interview findings. They revealed that the healthcare providers had discretion in determining when, to whom and how much time to assign, thereby exerting the power derived from their professional roles. Specifically, interviews with participants have shown that the primary obstacle to delivering effective Primary care services was the limited consultation time. A condition that hinders the provision of their optimal care and restricted General Practitioners from implementing patient-centred interventions or techniques. A simple comparison on consultation time parameter across the mainstream social worlds reveals that specialists from Secondary care and Community Services with longer consultation durations, are better positioned to foster stronger healthcare relationships with multimorbidity patients. In essence both social worlds serve as mechanisms to mitigate the effects of this systemic failure.

A final conceptualisation that emerged was that the notion of time extended beyond the 'arena' of healthcare provision for individuals with multimorbidity, and interacted with two other 'arenas': 'media' and 'preventive medicine'. Regarding the 'media' arena, two of its segments or otherwise social worlds are of particularly interest. These are the health policymakers and the commercial world of marketers. These contrasting social worlds compete for influence over individuals with multimorbidity, whereby time becomes the medium for achieving their goals. For example, while the commercial world aims to capture our immediate attention and prompt immediate responses to societal cues for immediate satisfaction of our needs, health policymakers face the challenge of redirecting the focus of multimorbidity patients towards long-term goals that require conscious effort, resources, and capacity (Samson, 2015). This adds further burden to an already burdensome situation. Within this context, 'preventive medicine' emerges as a parallel 'arena', intricately connected with the provision of healthcare for people with multimorbidity. A tangible example of the importance of preventive medicine in healthcare for people with multimorbidity can be seen in the significance of secondary prevention as a component of improved multimorbidity management.

6.3.4 Positional maps

As detailed in section 6.2.2, positional maps are the final stage in the analytic process of Situation Analysis. They aim to visually delineate in a democratic manner, the predominant positions taken and not taken (but expected to be) on specific dimensions

of the situation of inquiry as they emerge within the discursive data from the interviews with the project's participants (Clarke, 2005).

Critically, positional maps do not focus on people or groups but on all views expressed, no matter how diverse or marginalised, if they help to better explain the situation. The reason to transcend individuals and collectivities is based on the influential idea of Foucault to move research beyond the "knowing subject". It means moving research beyond thinking about knowledge as something possessed by particular individuals or groups (e.g., participants), and to consider how it was shaped by broader social forces like cultural norms, political systems, economic structures, institutional practices, ideologies and/or historical contexts (Clarke et al. 2018).

The number of positional maps required for a Situational Analysis project is not predetermined. It depends on achieving saturation within the situation of inquiry. In this final version of these 'analytical exercises', as Clarke et al. (2018) call them, a final refinement was undertaken to enhance their presentation. To achieve saturation several positional maps were created and can be found in Appendix 33. However, for brevity and readability, only the project map is presented and discussed here (Figure 8). This map conveys all important aspects that align with the pragmatic approach adopted for this project regarding the phenomenon of multimorbidity-multibehaviours. This serves as continuation of the findings from previous relational and social worlds maps.

Two critical dimensions are displayed on the positional map axes. The X-axis illustrates the spectrum of the iatrogenesis construct, which denotes the potential harm caused by implementing medical interventions, from total absence (-) to the highest risk of harm (+). The Y-axis illustrates the spectrum of the salutogenesis construct, highlighting factors contributing to holistic health and well-being, from full implementation (+) to no implementation (-). Salutogenesis focuses on creating and maintaining health by emphasising factors supporting physical, mental, and social well-being, rather than solely addressing disease or illness. Conversely, iatrogenesis is related to the unintended adverse effects of medical procedures or interventions.

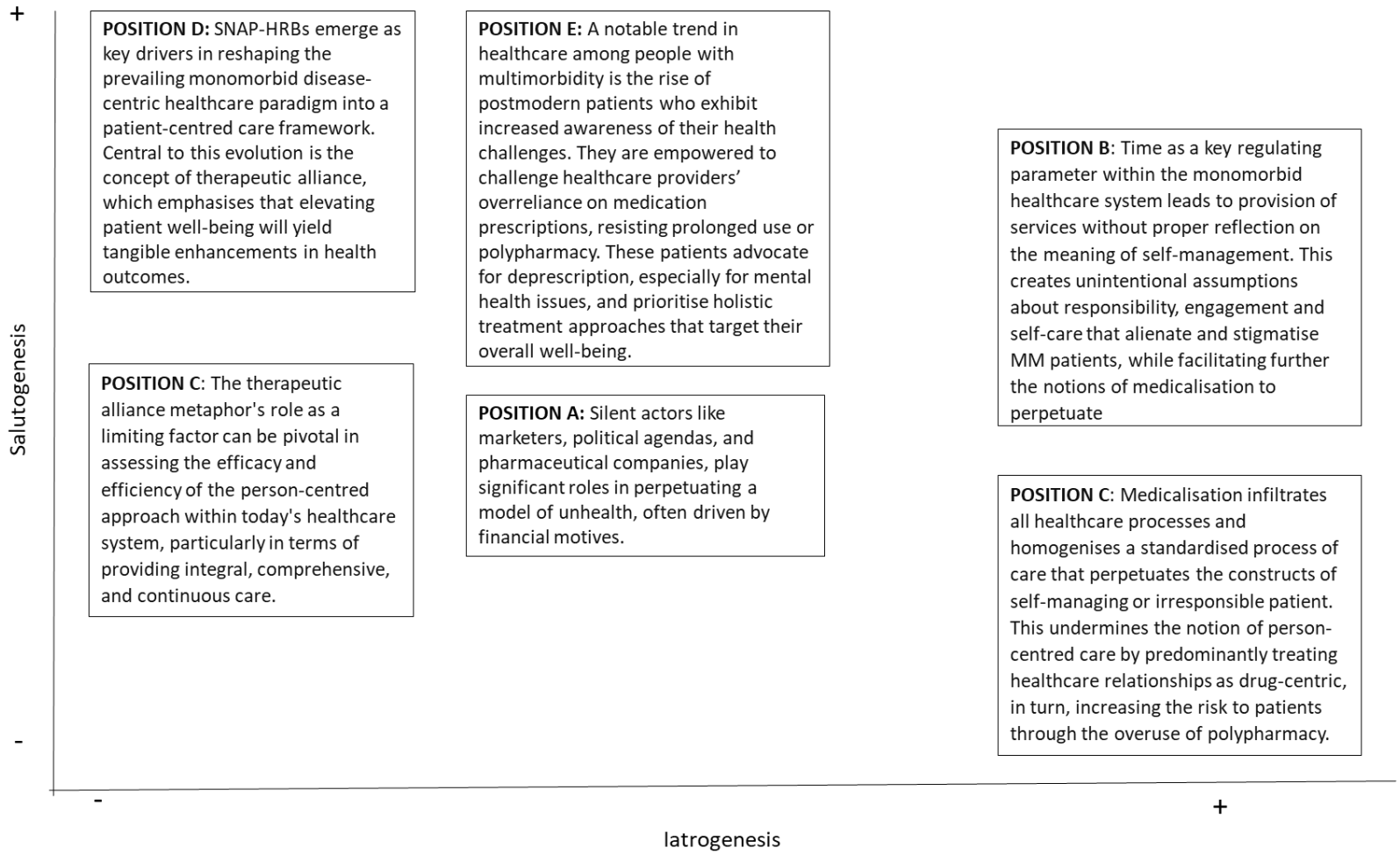

Figure 8. Project map of Situational Analysis

Six positions have been identified to offer a comprehensive understanding of the 'social' aspect of situation inquiry, addressing all nuances and complexities experienced by healthcare providers and people with multimorbidity in real-world healthcare settings. However, the present Situational Analysis project, being a monomethod approach, heavily relies on knowledge extracted mainly from interviews. Although daunting for a PhD study, to adhere to the suggestions made in section 6.2.2. regarding one of the primary objectives of a Situational Analysis project, particularly after presenting the project's in-depth analysis of the situation, the presentation of positions will be followed by extensive segments of participant interviews. This approach is considered as the best way to maintain alignment with Situational Analysis beliefs regarding democratic representation and the presentation of findings without oversimplifying the information. Oversimplification could risk losing the positionality, partiality, and the complexities influenced by postmodernism that make Situational Analysis distinct."

The scene is set by what Latour (2005), termed as "silent actors" (Position A), when referring to powerful influential social entities where, despite their absence, these actors wield considerable influence. In the present case, the marketers, those setting the neo-liberal political agendas, and pharmaceutical companies have been indicated as exerting power towards the perpetuation of a model of ‘unhealth’ often driven by financial motives. One participant stressed that:

> *“we need to take back some power for ourselves, you know? Not just go along with things. This is the problem, You think? Well, politicians should be talking about this, but all of them got these vested interests that, you know, they're all millionaires. They're all rich people they sit on board of companies. Well all these companies make money out of the fact that we're all disempowered. That's how they make their money (name of a company) is free because you're the product. You're the product on (name of the company). That's why it's free. And this dimension is the same for the healthcare. It is the same train of thought . I think for certain. So the unhealth of people makes money yeah, yeah, It does! It makes a lot of money They could promote you to be more well and they could have all these groups and closer communities and the doctors, you know they have to singed five years at the same surgery or something, but they’ve given less jobs to do so they got more time. They can improve this, surely get you more well, they're actually prescribing less stuff. Right! which means these companies meant less money and that connected with governments, lobby groups and all this , well, they don't want to make less money. I honestly think there is cynicism out there like this, they don't want to make less money, they want to make more money and they want to be all for them and screw everybody else. It's all going to be for me. How you deal with*

those people perhaps that's the question let's say, how do I promote? Being more empowered as an individual, that's part of the same question, is how to deal with people with that cynical" (P 15, 57).

This passage, apart from its reference to aforementioned silent actors, underscores three crucial issues which have also emerged throughout the interviews warrant closer examination later on in this analysis. Firstly, it highlights the necessity, for people with multimorbidity to be empowered to reclaim a degree of control over their health, rather than passively accepting the status quo within the provision of healthcare. Secondly, it addresses how their perceived 'lack of control' facilitates the provision of medicalised healthcare and through this a homogenisation of their health experiences.

Furthermore, time manipulation is a fundamental concept that shaped the functioning of modern society, affecting people's lives in various ways. For example, marketers through the extensive exploitation of media achieve to manipulate 'time' by deploying numerous conditioning cues that target instant satisfaction of our needs. By doing this, marketers can successfully promote products that either lead to unhealthy lifestyles, or medications that can reinstate a sense of 'health'. In either case, this manipulation of time towards immediacy overshadows healthy constructs, such as those targeted by NHS health promotion messages. Such messages often refer to long-term targets and goals that require more than a conscious effort to achieve, contrasting with the habitual reactions of marketers.

"Promoting a more generic, well, sense of well-being, exercise, eating more green stuff. Spending less time in front of the television. I mean, look at… look how many adverts you see at the moment on the television for (name of a company) and signing up for box sets etc. Like just in case there's the (name of a company) advert at home to solving you staying in is the new going out for a while and bollocks. You know, buy this new package get this new phone package and spend all night in front of the telly. Now they don't call them programs for nothing. You're... You know the sort of things that you watch, and they're are going to send you all sorts of messages that aren't helpful. You know, so again a balance, a balanced lifestyle to me is the way forward is, is something needs to be promoted. If you remember … they used to have an advert, you know? Mars a day helps you work, rest and play, a lot of bollocks, by the way, we just tripped off the tongue, but it… it was a good balance between, you know, work, rest and play. If you can think that you needed a split your life into those areas and balance it out, then you stand much more chance of being on an even keel. So, I think that a lot of health promotion, made by NHS is undermined by simple publicity" (P7-45)

In similar trend, manipulation of time (Position B) within the provision of healthcare services (from those silent actors like policy makers able to do so) appears to serve as a regulatory parameter aimed at producing cost-effective services. At least this is how perceived by those who develop and deliver services.

> *"the protocol (NICE single disease guidelines) is there because it's the most cost effective (clinical action) for the NHS" (P10d,117)*

However, the product of this approach reveals a systemic failure to provide services that adequately aligned with specific needs and concerns of specific patient populations, such as those with multimorbidity. An indicative example is the apparent lack of reflection among healthcare providers on the burdensome nature of self-management process for this group.

> *"Its constant. I need to think what I'm eating all day. Like I'm going to have breakfast and I do this and then and then I if I'm if I have a flare and then I take a different approach, I need to … lower my preconception and try to work on… my sugar and trying to eat more fruits and trying to do this and trying to eat less processed food and then I don't want to have any harm. And then when I got to the hospital and then I go to the GP and I have only 10 minutes and there they trying to explain for 5 minutes that I need to, you know, all the recommendations that I'm already thinking I'm doing. They've spent the appointment saying something that I already am working. I need them to do something else" (P10d-4)*

This systemic oversight usually leads to unintentional assumptions on questioning the motivation of people with multimorbidity regarding changing their unhealthy lifestyles or their responsibility for adherence to clinical recommendations for self-care.

> *"People's motivation is poor… willpower is poor and it's not easy" (P1-27)*

> *"I would say this depends on their motivation… They will often say that's down to my mental health. We would say that we can't prescribe motivation" (P7-13)*

Failure to adequately assess people with multimorbidity through inappropriate processes or protocols risks the alienation of the patient.

> *"I know I'm not in the 95% of the cases. I' m in the 2% and I know that as a fact because I have test in the past. I know I'm the 2% . It doesn't fit to doctors' calls" (P10d-4)*

This can lead to stigmatisation and perceptions of being judged among people with multimorbidity, who feel they are being labelled as irresponsible patients who make poor lifestyle choices.

> *"we quite often get where people feel judged, cause we know within weight management there is a lot of stigma and unconscious bias and where people have come into us and they said, well, the GP's just blaming it on my weight. So, he sent me to you" (P8-31)*

> *"I think I was judged …[that] I was making unsafe choices … they said my thought process I wasn't making safe choices… they were querying my capacity to make safe decisions, …. it makes me very worried for the future and me makes me because having some having had somebody question your mental capacity is quite worrying " (P9-24)*

> *"I'm quite annoyed really. I am. The NHS don't want to know and because my illness doesn't fit one of their boxes. They don't help me. I'm annoyed that I have to pay out of absolute fortune to see alternative" (P12-16)*

This often leads healthcare providers to struggle maintaining empathy, as frustration arises from systemic failures in implementing successful health behavioural interventions with the available resources.

> *They listen but they don't wanna hear, you know… don't see it's my job to nag people to, you know, they're grown up… They know what they're risks are, they can do what they want" (P1-16)*

As this approach to care overlooks the complexities of multimorbidity and multibehavioural factors, it's not surprising that individuals with multimorbidity-multibehaviours are often seen as presenting significant challenges to the current monomorbid healthcare infrastructure. This limitation hinders mainstream healthcare settings from effectively addressing the diverse needs of individuals with multiple and complex health conditions.

> *"if this person has the same complaints, actually need to get a slightly different treatment, because they're slightly a different sort of car engine, you know, and it won't work the same for everybody. But everybody gets treated the same" (P15- 6)*

> *"It's rarely ever, the medical condition in itself, that causes problems or yes, it can be challenging…That's why we're, we're specialists or, we're trained as doctors to deal with and there are different grades of doctors that can deal with that problem. But*

when it's not just the disease itself, but the added other things on top, the lifestyle, the risk behaviours that are added to the conditions that are making things worse" (P2-32)

"Chronicity… if somebody has maybe a recurring health factor that's quite significant because they could be well for a bit and not well for a bit. So, they can engage when well, but when they're not… you get the sort of the double whammy effect. You know, I don't feel well physically and I don't feel well mentally… you know, being assaulted from both sides… and it's difficult for clients to maintain focus sometimes if it moves from mental health and physical health… then often [we are] not quite sure where they're priorities are" (P8-22)

"There will always be social pressures, stigma… there's a lot of stigma. I think the stigma, aspect, aspect… exaggerates a lot of things because it keeps a lot buried under the surface.... So, any mental health issues that have been buried will come out somewhere. Usually at the worst possible time" (P7-34)

Within this system, the concept of medicalisation has emerged (Position C) influencing all aspects of healthcare practice in the monomorbid healthcare system. Medicalisation homogenises provision of care for all types of patients and prioritises a disease-centric, differential diagnostic system over individualised patient care.

"The only way of diagnosing it is from process of elimination… There is no fundamental approach to giving you that diagnosis. It's just "you haven't got this, this or this, so you must have this", you know?" (P12--4)

"they just say it's inconclusive…. That's their favourite word. And they say, "oh, it's inconclusive. We don't know what's wrong". And there's been no conversation about this symptoms or... how things have been progressing… You just go in, the test takes place, they don't tell you why, they don't tell you the results. It's just a fruitless exercise" (P12-35)

However, focusing solely on morbidities and their symptomatic thresholds neglects individuals who fall outside the scope of the differential diagnosis process. Such an approach risks missing timely diagnoses and appropriate treatment differentiations that could be realised through implementation of person-centred care techniques within the healing relationship of healthcare professionals and multimorbidity patients.

"if this person has the same complaints, actually gets a slightly different treatment, because they're slightly a different sort of car engine, you know, and it won't work the same for everybody. But everybody gets treated the same" (P15- 6)

Thus, within the medicalisation context healthcare relationships are predominantly viewed through drug-centric lens.

"No, no, nobody really checks on what you're what you're eating or how you are eating or whatever Just on medical terms, nothing about dietary at all" (P13-17)

"There's not the support there, for the anxiety and depression ####, councillor which just, you listen all they do then is just throw the medication at your and there's no nothing else. No with the support" (P1c-137)

Something that, in the end, undermines any notion of person-centred provision of care perpetuating the dichotomy of successfully self-managing multimorbidity patient versus the irresponsible one.

"So sometimes it's hard for me to go to the health care professionals. And the first things I they think is I'm going to give you this. I'm going to give you that and I don't want the medicines. I want other things... I want suggestions about how to get my sleep better, how to care for my skin with different patterns... But the truth is that nobody knows… or they don't have the time to go and sit and find and research" (P10d-15)

"They've got capacity. They're just gonna get on with it. So then you have to say, "well, that means I might have to prescribe more medication for you" or more diabetes medication or more inhaler therapy or something like that. So, you can only knock people so much and then you have to let them get on with it. You know … it doesn't make it difficult, it just makes it a bit frustrating, you know, or you just have to reach for another tablet or, you know, "I'm afraid you're gonna have to start on insulin, if you don't lose a bit of weight" (P1-16)

Consequently, this increases the risk to patient safety through polypharmacy and/or drug adverse events.

"They'll have lots of potential drug interactions or beyond, you know, half a dozen or a dozen medications. So that's always difficult. So it means if you… add another medication, you may be limited as to your choice of medication because there will be an interaction with your favourite first choice medication, so you'll have to choose something else… So drug interactions is a big thing. In multimorbidity people who are on lots of medications and lots of them are on lots of medications, follow up is a little bit more complicated" (P1-8)

"the community, dermatologist is … … But when I went there he wanted to 'push' the normal steroids they put on everybody and I was like "I can't have that because that has these components. You have a report on the system that… I don't know if you have read or not… but you should have. If you were seeing it, it's saying that I'm allergic to four components that are mainly in the medicines that are used for treating the skin, so you need to really search better for medicines that are suitable for me, because if not, I'm going to get worse". And then he was like "oh you are a difficult, you are a difficult patient" (P10d-120)

"the neurologists don't want to know about my new pain. The haematologist only wanted to know about my blood. There is nobody who was overseeing it in holistic way. So, the neurologist could have given me… lots of nerve killing drugs. Haematologist may have given me something else. But none of this is fixing the root cause" (P12-26)

An indicative example of how 'medicalisation' and 'time' constructs have been internalised by people with multimorbidity, highlighting their role as implicant actors, is evident in the omnipresent socially internalised narratives within the healthcare contexts. Two such narratives, such as the 'magic pill' or the 'quick fix' carry with them significant symbolic interactional meanings denoting how the notion of 'time' (implicant actant) has served the establishment of the notion of 'medicalisation' (gaze) as the driving force of healthcare provision.

"when you then have patients who are deliberately not, you know, either carrying out health and health risk behaviours or insisting on going on with the lifestyle that is, that is adverse to their condition, is not making things improve and they have to keep coming back to you as though you would have like a magic pill that would sort the problem. And you keep adding on medication or tweaking their medication" (P2-21)

"an awful lot of people come to us wanting a quick fix and I have to explain in as gentle terms as possible… "we can show you what to do but it's up to you to do it". [So] We would try and motivate people. So, all we can do is show what the best way forward for them is by putting in, for example, small steps, small exercise steps, you know, today we'll go for a walk around the block. Tomorrow we'll go for two walks around the block. And slowly but surely wins the race and. It's a long… slow challenge sometimes…if a person really understands that they've been maybe participating in a lifestyle for probably a couple of decades. You know, it's not going to do a turn overnight, but that's what a lot of people seem to want… there is no quick pill to make it go away" (P7-21)

Therapeutic alliance (Position C) has served as the key metaphor for assessing the integration of person-centred approach within the mainstream healthcare settings. As argued, the relationship between healthcare providers and patients with multimorbidity can offer an invaluable framework, for exploring and discussing the concept of behavioural change (Keyworth et al., 2020). It can also act as a 'limiting factor' (Meadows, 2008) in identifying potential systemic failures of introducing person-centred care and, as such, effective health behaviour change interventions within the provision of healthcare for people with multimorbidity.

The first concept under examination refers to the Integrality of care, which essentially involves adopting a holistic approach to care. This approach encompasses not only addressing morbidities but also attending to aspects of overall well-being.

The most evident finding was the transformation of the consultation process, to a 'box ticking exercise', mainly due to the time constraints imposed on healthcare providers to meet the Quality and Outcomes Framework (QOF) criteria, while simultaneously entering QOF data during the clinical interview. However, this clinical process leads to the alienation of both parties involved in the healing relationship, obstructing the establishment of any therapeutic alliance.

> *"it's a tick box exercise, you know… what I've got to do is write my little text box on the screen and cover my arse. That's the mechanism of it. I feel that for whatever reason I'm blind to you" (P15-28)*

> *"you can feel all is very computerized. It's mechanical" (P10a-2)*

> *"Everything is very much a sort of an algorithm. In fact, you could probably have a computer do most of what the doctor did, you put enough yes and no's in boxes and come up with the answer. They've been told, you have to go in this framework, follow that flowchart, do this. So, actually bringing their own intelligence to bear. I don't think they have a lot of opportunity to do that. I think they have to follow a flowchart or an algorithm of what the treatment pathway is according to the NICE guideline, or whatever, and if it triggers that, you do that "(P15-11)*

> *"The biggest thing I find is communication. People talk, they don't listen to you. …. If they if they listen, and take on board what you say, … I wouldn't have gone home and been in tears on a Saturday night because I was in that much pain" (P13-21)*

"Maybe those protocols work for most of the people and most of the cases that… are having just one condition or are just presenting with an acute thing, but maybe this isn't an approach that can be taken for people that has multiple things or more complex things. So can they do an assessment of what are those conditions "(P10d-122)

Within this context a consequence of the aforementioned consultation process provoke, people with multimorbidity to perceive the healing relationship as merely a prescription process, detached from addressing their actual needs.

"Because they have protocol. I saw them open the books and see what is the... dose or something" (P10-1-119)

"The protocol is not for me. The protocol is for the doctors as a guideline… but [I] need something more… someone [who] can understand better and can give us back solutions (P10-1-131)

It is this lack of personhood that is perpetuated by the current one-size fits to all approach to consultations that drives people with multimorbidity to seek alternative solutions, sometimes resulting in risky decisions that jeopardise their safety.

"I'm quite annoyed really. I am. The NHS don't want to know and because my illness doesn't fit one of their boxes, they don't help me. I'm annoyed that I have to pay out an absolute fortune to see alternative" (P12-16)

"I stopped [medication] by myself. I did it slowly and in stages. I didn't ask the doctor's permission, I just decided I took this for six years. All of these drugs have health problems if you take them long term. So I thought I've got to stop taking this, I will go and buy something else purely for that reason. So I went to the doctor and they said, right, try this amitriptyline. So I'm trying that now. But what I noticed was, after about 10 weeks of not taking the Sertraline, I started to feel a lot more pain, sort of muscular, and just body pain" (P15-17)

Cultivating a deeper understanding of the experiences and individuality of people with multimorbidity within consultations, instead of strictly following mechanistic procedures, can help prevent such avoidable scenarios. This situation often arises when individuals with multimorbidity are referred to secondary care or community services.

"We'd have a look at kind of what's what are they referred in with and what is the most pressing concern… if somebody has diabetes and they're having lots of hypos, that to

me would become a priority because that that could indicate quite a critical acute risk. So I guess I would be looking at what events are in place that could result to an acute risk. You know, how can we mitigate those, but at the same time you're addressing the health behaviour, so it would be then looking at kind of the education … it's addressing with the individual where they see that priority and where I see that priority and does that match, do they understand, you know why I might be concerned about it and how do they feel about it." (P7-3)

In this effort the construct of 'time' again seems to be the most pivotal parameter toward this goal.

"[I] want a very big appointment with the GP. I need a big appointment, three, four five appointments in the row maybe [and a] more human approach to me as a GP! (P10-1)

"Yeah. I agree. Time and more human behaviour" (P10a-2)

"Yeah, we need more time. And the… the pressures on our, our service are fantastically great" (P7-21)

When proper consultation time secured allows the implementation of more person-centred care (e.g., implementation of 5Ps model).

"I'm I look holistically. So it's not just what you're presenting, mental health symptoms… no, it's what are you doing on a day-to-day basis yourself… do you spend all day in bed, do you spend all day on the couch playing Xbox, or watching the telly, or can we do a little bit of exercise, and a little bit of self-care, and a bit of maintenance which can help you or enable you to move forward in your own mental health. So I don't just focus on symptoms or feelings. I'll look a little bit more in depth than that. We, we work on what's called the five P's model, presenting symptoms, predisposing symptoms, that sort of thing, which does cover some of that. And it's not a bad model to work from… a recovery, gently challenging approach" (P7-4)

Within the consultation settings, there was a greater potential for the development of an agreed care plan, another parameter of Integrality of person's care, with action plans tailored to their range of convenience, ultimately benefiting their overall health outcomes.

"the things that I noticed when people have multimorbidity is… I used to ask in my in my clinical role about how well somebody feels at the moment and it would be quite

interesting … you know how did they rank their health on a scale of zero to 10. Because this would be part of my motivational interview, you know, finding out and then I would ask, you know, well, what do you think would improve that?" (P7-1)

Then, more people with multimorbidity than not, according to participants have been found to follow the recommended changes.

"Depression and loneliness and boredom, comfort eating, emotionally eating is a really big one. Uhm and as I mentioned about time and sometimes a lot of these can be addressed when we look at planning… planning ahead for these kind of barriers" (P724)

"So if you tell them things that are within their reach and that they have control over and they can actually do to help their condition, I find many people are motivated to do it. It's only when you're asking for something that they feel is possibly out, you know, much more patients than, than not, are willing to try whatever it is to help themselves feel better and get…had this quality of life that they can" (P2-32)

However, systemic limitations within mainstream healthcare settings, such as fixed-time appointments, seldom allow for the implementation of consultation models that facilitate co-production and acknowledge the lived expertise of people with multimorbidity as equal to that of healthcare providers. Instead, models such as additive sequential decision-making that prioritise urgent matters (leaving the rest for future consultations) or guidance-cooperation models that place healthcare providers in dominant positions, are most commonly implemented. This seriously undermines efforts to effectively implement person-centred care.

"Bearing in mind we've got 10-minute appointments, so you've got to focus on what you're gonna address in that in that particular time frame. And often it's just a case of dealing with the problem that they presented with" (P1-8).

In essence, prioritising episodic care creates a gap in the continuity of care for people with multimorbidity, hindering healthcare providers' the ability to understand their comprehensive patient history and assist them in managing their health concern.

"There is no follow up. If you don't call them. There's no follow up "(P10-4)

"not really because you're seeing different ones. you never see the same one twice… every time you went to the GP, it was someone different" (P10-3)

"They diagnosed, but they don't have any history to go on of how to manage the illness" (P12-19)

The responsibility for ensuring continuity of care, the second pillar of the therapeutic alliance metaphor, falls primarily on Advanced Nurses within Primary Care settings, affecting not only individuals with multimorbidity but also those with chronic conditions.

> *"most of the chronic disease management now is done by Nurses, what we call advanced nurse practitioners, healthcare workers. So they will do most of the health promotion". (P1-4)*

Nevertheless, the formation of these annual checks does not meet the complex needs of people with multimorbidity, making them feel that, rather than a therapeutic alliance, the consultation moves towards pharmaceutical treatment.

> *"You get me appointments [every] six months with the asthma nurse and that's it. That's all I get… but it's like a picture of that day is not like in the last six months ….That day six months later and you're down here and nothing from the GP about anything. They repeat prescriptions and that's it… Nothing else. "Usually give focus to medication and ask for … the annual exams. So, from the whole year I start to take the new medication, until the next one, ... So, between all this time… Maybe need something to change. And really, I don't know. I feel very unsupported in this time". (P10a-1, 3)*

Furthermore, the contradictory interests and needs between the two parts of the healing relationship, as placed within the specific context of monomorbid healthcare system, make both parties feel that it is a one-way healthcare relationship.

> *"You know, we can only do what we can in that case. The patient also needs to… give and take some responsibility" (P2-35)*

> *"last year I went to the GP… my surgery said that… I know this is mental health related and I need help with that uhm, she was like, "I don't know what to do. What do you want me to do?" And then I needed to lead what I thought was my care. But in the back of my head, I think "I'm not that I'm not a medical professional I and I'm coming here especially when I have exhausted everything I can do at home and I'm looking for something else that could be done" (P10d-4)*

The impact of such developments is far more severe for people with multimorbidity, who are eager to have a therapeutic alliance that permit them to discuss their health issues holistically and outside the 'protocol'.

"Outside the computers and then robotic things or like protocol, something like maybe more than the protocol. Because they have protocol. I saw them in the open the books and see what is the, you know the dose or something. Something out of the protocol. Something more. For me is to see the forest not only the tree" (P1-82)

"No. The protocols …how do I put it, it's, it's not the only solution, the protocol is there because it's the most cost effective for the NHS. There is the risk of the situation and then this is a protocol" (P10d-118)

As such the establishment of steady healthcare relationship between people with multimorbidity and one main healthcare provider (preferably their General Practitioner) has been regarded among the bigger systemic changes that could be achieved.

"Isn't it obvious that your GP is the most trusted person for you". (P10a-120)

"think seeing the same patients and having some understanding of who they actually are, would make a massive difference to how the doctor could operate [because] you know, you feel that you want you have a responsibility for the people that you're looking after, because it will be you next time, you won't be able to see this person again. Now, next week, or next month, they're going to come back to me. And I'm going to be the volume. It's the next decision and decision afterwards. So, my decisions matter now to me personally, and I will be accountable for them" (P15-39)

The final dimension emerged from the examination of therapeutic alliance metaphor in the healthcare relationship (between the people with multimorbidity and healthcare providers) is the integrated-comprehensive care. This entails a spectrum of services available to people with multimorbidity as well as the means of fostering collaboration among various healthcare providers to function as a cohesive multidisciplinary team.

The initial concern highlighted here underscores the fragmented nature of care experienced by people with multimorbidity and their healthcare providers. This fragmentation is evident in the main navigation policies of referrals and signposting, which lack evidence of any subsequent intersectoral coordination or collaboration following their implementation.

"we do refer patients for this activities and you know for patients who are overweight, obviously you need to refer them either to have an exercise" (P5-4)

"so, if you've got somebody being treated by an acute specialist team and you're working in a community team, you won't necessarily can't necessarily see it's difficulty as well with sometimes if bloods have been taken by one hospital, you can't view that

hospitals, bloods. If you're trying to see what they're cholesterol is or though their HBA1c and so there's challenges in that respect" (P10-3)

"there are a lot of other loopholes that needs to be bypassed… in an ideal situation we, we could do with breaking down those loopholes, making it more smooth" (P6-16)

"there are big gaps for every steps and for every step…. fragmented…Yes. At the end … I wasn't well. So, I lost these big chance to have this, uh, support to push me to face my problems and want this change into my lifestyle" (P10-1).

At times this is intensified due to healthcare providers inability to navigate, either via the provision of reliable information or practically supported, their connection with needed services.

"None was asking for social prescriber none advise me for that, because from a friend I knew from social prescriber things yes mouth to mouth. Yes, for a friend Uh. I asked him to speak with the social prescriber "(P10a-1)

"first of all, communications between services and teams and trying to find sometimes what patient might tell you what somebody else has told them. I can think of some funny stories. It is not quite what they've been advised" (P8-7)

"In my case, we only learned that with this dermatologist because we went to A&E and we're in the hospital for one week. The GPs never heard about until they the dermatologist go back a letter saying I see these people in the A&E and everything. This is how you we want you to take care. So, if they ask for this medicines, give them the repeated prescriptions. If they ask for, these are the other …. do this and do that" (P10-4)

While at other time the fragmentation of care becomes apparent due to healthcare providers' inadequacies in medication management.

"I want them to start a certain medication… in an ideal situation I should get in touch with the pharmacists for example in the community to say I want my patient to be settled on this tablet straightforward. But the way the system works is that I have to write to the GP, who would then get in touch with the patient and the pharmacist to prescribe that? So, for someone who's good at comorbidities, who sees a heart failure specialist a rheumatologist, the kidney specialist, you can imagine how many times they're having to go backwards and forwards to deal." (P6-15)

Establishment of an intersectoral multidisciplinary team has been suggested as an effective way to simplify care delivery. According to the literature, such a multidisciplinary team could be highly beneficial for the effective treatment of multimorbidity patients and the acknowledged complexities that accompany their health situation, either by reducing the number of appointments needed with various healthcare providers or reduction of polypharmacy and associated risks of adverse effects (Smith et al. 2012). However, despite its significance no such evidence was detected through the interviews. One explanation posited relates to the lack of General Practices to provide the requested services.

> *"that's quite important, engaging someone like a psychologist or even a dietitian, someone who helps them change their behaviour. I think that would make their management more effective because there would be that extra support that they need to change their habits, to embrace more health seeking habits. But the problem is that… not all GP surgeries offer those services. OK, so I might say to a GP surgery… "can you please refer this patient to a physiotherapist who can give some advice on some exercise for this patient or a dietitian who might be able to give advice". But not all surgeries have that service." (P6-7)*

A final issue regards the comprehensiveness of care and, specifically, access to Primary care for people with multimorbidity when needed, given that this population is particularly prone to acute health issues. However, the current practices and policies focus on 'equality' in access via the Triage system, which pose another barrier to quality care provision for people with multimorbidity.

> *"I decided to ask for specific doctor who is in diabetic specialty. So they sometimes they said that he didn't have any other appointment in the next 3-4 weeks… So this is a very big problem [MM]" (P10a-12)*

> *"Sometimes they have to wait for ages … for GP appointment Sometimes they have to make [up] stories to have an appointment. Exaggerate things" (P4,45)*

> *"I went to the reception as soon as I got this appointment. I said, "look, I really need a double appointment because I think I may have arthritis in this". And could I have a double? She looked, "No, no, no double appointments available". So, I said, "OK, what am I supposed to do now then?" So, she said "we have a physiotherapist who comes to the practice sometimes. I'll book you in to see her on the 15th of May"… By the 15th of May, what, 18 months after… And I have said to them, look, you're gonna have deaths*

on your conscience because I'm reasonably fit and able to ring, … but … if they'd be people worse than me, the poor things will be dying" (G-15)

The greater challenge to addressing the present situation regarding the provision of healthcare for people with multimorbidity appears to stem from the inclusion of SNAP-HRBs (Position E) as a standardised assessment and intervention process. However, as grounded discursive evidence showed, SNAP-HRBs represent the 'elephant in the room' regarding their role in healthcare delivery for people with multimorbidity.

"They sent to me a pamphlet from the dieticians at university hospital. When she came to see me in hospital, she didn't have any pamphlets. So, she sent me one in the post. Now to me that's me, that's pretty bad. You know you're trying to help people get better by what they eat. But you haven't got the information" (K-15)

There is general recognition of the pivotal dual role of SNAP-HRBs as contributors to and moderators of multimorbidity risk and management. Yet their inclusion in standardised processes for assessing and intervening in multimorbidity development or management is inconsistent within mainstream healthcare provision. This discrepancy is particularly apparent in primary care settings, where the delivery of comprehensive care is crucial for effective multimorbidity management. Similarly, non-standardised inclusive processes for SNAP-HRBs were also absent in secondary care settings, highlighting the normative power granted to healthcare professionals in choosing what kind of interventions to offer, and to whom. When asked about if they ask people with multimorbidity questions about their lifestyle or questions during routine health consultation:

"Uh, not routinely, but if, If I think it's pertinent. So, if somebody comes in with an exacerbation of asthma... I'll ask uh about a smoking history. If I think they're a bit overweight, I mention it. Um, if they've got gastrointestinal problems or they got abnormal liver result, then ask about or overweight, ask about alcohol consumption, that sort of thing. So, I won't ask about everything. In every consultation". (NP-1)

"It depends on the patient's condition" (SP2 -1)

"Whenever we meet patients, you know, they come to me mainly with a liver related conditions. But if they are coming to clinic, we ask them specifically as it is part of the history taking, if they've got any health risks, behaviour like smoking and alcohol" (P3-1)

"For every new patient I ask about lifestyle. It's part of my way of trying to know more about them and trying to come to a diagnosis of their problem. So routinely, every new patient I see, I go, I talk about their lifestyle. When you come to their reviews[(at hospital with specialist], patients are already known. It depends on what their problems are" (P4-1)

This perpetuates the medicalisation of care, creating a 'safe mode' scenario where healthcare professionals prioritise medical issues over SNAP-HRBs within the treatment process. A dynamic was acknowledged even by numerous specialists without medical backgrounds (e.g., community occupational therapists. This is despite the wide acknowledgment of the health benefits of well-managed SNAP-HRBs for the well-being of people with multimorbidity, and their significant effects on various health outcomes.

This is further complicated by the numerous socio-cultural barriers that intervene within the healthcare relationship, which might relate to patients age and gender, health literacy, lack of accessing, cost etc.

"So sometimes young people who are comorbid may find it hard to find a healthcare professional they can trust. And I think part of it is the struggle that they have with dealing with multiple comorbidities and how restrictive that is on their lifestyle" (P4-7-9)

"I found it different between men and women... I can't generalise, but I'm just saying… I've heard a lot, a lot of women will have said to me, "I just don't have time for myself". Uhm, they put themselves last. They're looking after maybe dinner for the husband, cleaning the house, picking up kids, taking the kids to school activities.…their priorities come last. Don't get that same family demand response from all the men or, you know, from lots of men. Occupation can be a big driver for it. I've seen quite a lot of uhm, lorry drivers, distance drivers. Who will say, "oh you know, people who work away… they'll do really work long hours, so when they come back home, they are exhausted, and this affects their food choices" (P8-22)

"you educate them… we find out some of their lifestyle habits and you're like "these things are not helping you know you need to get more active; you need to cut down your sugar you to cut down your salt"… and you give them all these tips, but you find that they're not. And they're not following in some [cases] because of other circumstances. They don't have access to healthy food. They have hip pain or problems going on in their joints… They can't have access to nobody to take them to the gym, it's too far away from them to do swimming because that's the only exercise they can do.

So in some cases, it's totally out of their hands. They're stuck in a rut, and they have to carry on in that lifestyle, and because that's all that's available to them" (P2-14)

"The main problem really, is financial... I am on a small pension. I do work part time. And again, I try and eat as much fresh food as possible, and the doctors have said not to eat processed food. Unfortunately, sometimes I don't have a choice because of the finances, cause fresh food is more expensive than processed" (P11-7)

A crucial product of failing to integrate the SNAP-HRBs into the provision of care relates to the lack of care planning that targets behavioural change based on agreed specific priorities.

"If you're looking at the behaviour change, to address that, I think it's really important, and I see this a lot where people come in and they haven't maybe been given the education from an early point to understand why people are concerned about it. Next, I would be looking at finding out [the] priority for them because when you're looking at behaviour change you, you're looking at what's their agenda, what's most important to them. Because for a lot of the things I see within weight management, if we can address the weight management, a lot of the other comorbidities will improve at the same time" (P8-12)

A situation where traditional models, such as the assess and advice model, are typically applied as health promotion strategies in mainstream healthcare settings

"We can only advise on healthy lifestyle" (P-12)

"the only … intervention I do really is, is giving them advice and being very specific about it. And sometimes it comes down to being quite practical on suggestions of what they could try if they're finding it very hard to know where to try" (P6-3)

These approaches are ineffective ways to introduce behavioural change processes, especially in those not ready to change, as well as inefficient to reach with low health literacy, and those known in behavioural change literature of 'precontemplators' (i.e., not yet considering making changes to their behaviour).

This directly implies that the general standardised process of healthcare provision for people with multimorbidity who engage with multibehaviours is susceptible to the

inverse care law construct: it fails to secure the provision of the optimal care for a number of patients who most need it.

> *"I remember one particular lady who had said her diabetes nurse had told her that she needed to eat biscuits to stop going low. And when I eventually did kind of catch up with the diabetes nurse, through her consent to that… that wasn't the message that had been delivered to" (P8-8)*

This situation not only creates frustration for both parties of the healing relationship, but it also creates misconceptions that perpetuate this problem and exacerbates a fear of not imposing unwanted lifestyle changes on people with multimorbidity risk.

> *"No, because here they respect too much your decision. They …. don't …advise, it's not about pushing your boundaries, offering all the options" (P10b-2)*

> *"they have hip pain or problems going on in their joints. So, exercise is totally out of it for" them (P2-14)*

> *"You can inform them that obviously smoking and alcohol, as they say, is not good for your health, [but] you can't tell them not to do it. Everybody's got [a] right to do what they wanna do, but we as professionals are there to support persons and whether I think that smoking or drinking is not good for you is my belief… so I can't push that on to anybody" (P4-12)*

It also perpetuates unintended forms of prejudice and stigma, even those related with misperceptions regarding health-related barriers that prevent implementation of specific health enhancing behaviours.

> *"they don't seem to offer anything about depression. They sent me to see a counsellor. And all she said was "Oh, you need to you need to get out and join some, other… 55 club, you know, like do things". Uh, I was 48 at the time… and that was it, she says basically, I felt like she was saying [I was] on my own. Now folks going to think that I was, you know what I mean? And I never went back again. It just completely lowered me [more] than I already was. Like it made me feel even worse. She wasn't listening to anything I was saying. I needed to lose weight. I did actually lose…. But that didn't help me with my asthma cause my… asthma is mainly caused by allergies …even when I lost that weight, my breathing was just as bad… I found it hard to exercise cause even walking up the stairs…really … out of breath (P10-3)*

Motivational Interviewing has emerged as an effective alternative for introducing behavioural changes without imposing them. This is crucial given the challenges associated with healthcare interventions for people with multimorbidity. It suggests that a collaborative framework for delivering care addressing both multimorbidity and multibehaviours could not only be feasible, but potentially effective in enhancing the well-being and health outcomes of patients with multimorbidity. Unfortunately, failure to fully integrate SNAP-HRB interventions into multimorbidity care is directly linked to drug prescription practices and the issue of polypharmacy.

> *"There's no point in me saying, well, actually, that you know, "this is what you should be doing"… if there's some kind of barrier towards that. So, exploring first of all, what is their understanding? What do they think they need to do? And if they say, "I know what I need to do, but I don't do it"… then I would explore, "Well, what's stopping you?" And then we would go through the barriers and maybe kind of chat it. So, it's a bit more… I would move away from the clinical treatment type thing and move more into kind of motivational interview and understanding from where they're coming from" (P8-16)*

However, a noticeable trend is emerging in the healthcare of people with multimorbidity as identified through the present interviews: the rise of postmodern patients with multimorbidity who are increasingly aware of their health issues.

> *"the NHS, no, there's no conflict because they don't have any information. Umm, if you research online, which I do, a lot of the university research states that magnesium is lacking in ME patient so. I take magnesium. And that helps me massively. So, I followed the advice of the university research. But generally, the NHS Trust has no information… They've actually said to me that [I] seemed to know more about my condition than they do because they don't study it and I do". (P12-12)*

> *"I went to the GP last time with my eczema. And I said "I just want you to listen". And I sat down… talking nonstop for 15 minutes… because I don't want to take steroids. I really had bad reactions to steroids in the past. And then when I stopped using the steroids I had, like a flare. But I got better, and I know I can be better in my health without the medicines". (P10d-15)*

These patients found that they were able to challenge healthcare providers' overreliance on specific aspects of medicalisation , particularly when it comes to medication as the sole focus and outcome of the consultation process.

"GPs all the time asked me about the medication, they never asked me if I am active enough or if I have gained weight. So now I'm telling them to look. I have gain weight and I feel I need to lose this, Uhh as a diabetic I need to be more slim or something. So from the time I I've started to ask for more support, more support, just the referrals comes to me" (P10a-28)

Furthermore, this particular type of multimorbidity patient is resistant to prolonged use of medication and/or polypharmacy and generally averse to turn their healing relationships with the healthcare providers into pharmaceutical relationships; a safe harbour for their healthcare providers to be totally absent.

"they're worried about making me worse. But in in being worried about making me worse, you're not making me better either" (P9-39)

These patients advocate for more de-prescription, especially when addressing mental health concerns, and seek more holistic and empowering treatments that prioritise their overall well-being as the pathway to better health.

"if you're going to keep us alive, then it has to be a level of quality of life, not just you are alive "(P9-40)

6.4 Discussion

6.4.1 Main findings

While multimorbidity is an extensively addressed health phenomenon in public health and policy discourse, less emphasis has been put on its joint impact with multibehaviours on healthcare system. On this basis, the present study was the first to examine the combined impact of multimorbidity and multibehaviours on the health professional-patient healthcare relationship.

Employing the comprehensive analytical exercises of Situational Analysis, this study revealed the conceptual framework of Salutogenesis and Iatrogenesis dipole, as a way to enhance our understanding of the situation. Within this framework, it was found that medicalisation and manipulation of time within healthcare settings, where services are structured to meet cost-effective quality criteria, pose risks of medical adversities. Conversely, factors such as SNAP-HRBs and the post-modern patient and therapeutic

alliance metaphor can act as countermeasures, shifting the provision of multimorbidity care toward a holistic health and well-being approach.

Applying this analytical framework, key finding centred around the notion of self-management. It revealed how the joint impact of structural and functional systemic deficiencies has led to an increasingly iatrogenic healthcare system. Consistent with literature, the identified challenges primarily revolved around the daily management of the predominant morbidity or symptoms, drug-related concerns, coping with pain or other physical symptoms, time constraints, financial burdens, insufficient communication, or miscommunication with healthcare providers (Jeranta et al. 2005; Sathanapally et al. 2020). Barriers revealed by the present study and supported by existing literature, prevent people with multimorbidity from implementing necessary lifestyle changes associated with their multiple chronic conditions. These obstacles arise either when lifestyle modifications appear incompatible (e.g., dietary changes exacerbating stoma issues) or when adjustments for one condition interfere with self-care practices of another (e.g., reluctance to engage in physical activity due to asthma concerns) (Bayliss et al., 2003). This has been described in terms of an “endless struggle” Turabian, (2019, p.87) of daily adjustments to numerous, and often contradictory, multimorbidity management decisions.

Despite the well-documented burdens associated with multimorbidity, it has been suggested that healthcare providers are found to frequently overlook these challenges, oversight to often leading to unintentional assumptions regarding the motivation and responsibility of individuals with multimorbidity for their self-care (Bower et al. 2011). Consequently, this failure to acknowledge the burden of self-management among people with multimorbidity results in stigmatisation and feelings of being judged, further alienating individuals from the healthcare system and the services designed to support their self-management (Valderas et al., 2010). Findings that have corroborated within the present study.

Examining this phenomenon at a structural level, an alternative ‘social’ explanation can provide insight into what may seem an oxymoron to aforementioned findings. By employing the sensitising concepts of implicant actants, Situational Analysis uncovered the structural manipulation of time. While it is true that multimorbidity poses a challenge to healthcare systems worldwide, prompting a response to adapt healthcare

resources to this new reality (Turabian, 2019), time manipulation during neoliberal reforms achieved the opposite effect. As a result, reforms aimed at consultation times failed to provide the quality of services flexible enough to meet the diverse needs of different types of patients, including the subgroup of patients with multimorbidity. A possible aftermath, serving as a counterbalance, is the emergence of the notion of (ir)responsible self-management by patients (Lawn et al., 2010)."

The UK is among the countries to apply such reforms to their system (Jasso-Aguilar, 2015). This assumption gains credibility from the compelling argument put forth by Lawn et al. (2010), who stressed that it is "unlikely to be a coincidence that self-management has been born and thrives in neoliberal states" (p.7). By promoting the persona of the effective self-manager for people with multimorbidity, there is less pressure to develop healthcare services that truly reflect the essence of self-management and optimal care; e.g., longer consultations to allow implementation of effective behavioural change techniques like motivational interviewing (Levenstein et al 1986) or personalised care plannings (Coulter, Roberts, Dixon, 2013) toward those needed lifestyle changes. Consequently, by perpetuating the assumptions of (ir)responsible self-management, healthcare providers unintentionally alienate and stigmatise those with multimorbidity who do not effectively adapt to these new circumstances, despite have the greatest need (Kamerow, 2012). The paradox probably stems from people still believing in the effectiveness of these services, especially when even supporters of neoliberal reforms admit their obvious weaknesses. It seems that healthcare reforms, like the ones mentioned earlier, might have gone too far. (Jasso-Aguilar, 2015).

Another issue that emerged by employing the Salutogenesis – Iatrogenesis dipole regards with the overarching discrepancy concerning the limited evidence that person-centred care in is used in practice. This was particularly notable when it regards the application of person-centred theoretical principles to the care of people with multimorbidity. This has been a primary concern in numerous related studies examining various aspects of multimorbidity healthcare (Little et al.2001; Sathanapally et al. 2020; Moody et al. 2022). Applying the therapeutic alliance metaphor as a ‘limiting factor’ (Meadows, 2008) within the framework of the Salutogenesis-Iatrogenesis dipole, the current study identified potential systemic shortcomings in implementing person-centred care. These shortcomings directly or indirectly affect the effectiveness of health

behaviour change interventions within the provision of healthcare for people with multimorbidity. The present study revealed several disparities between theoretical principles and practical application in real-world settings. Such disparities prevent the transition of multimorbidity care from its iatrogenic origin toward a more salutogenic approach. The identified discrepancies regard fundamental person-centred principles such as integrality, continuity, and integrated delivery of care.

In short, none of the aforementioned person-centred principles observed in the present study fulfil the criteria. A finding that supported by the literature review. For example, it was observed that limited fixed-time, single-disease-based consultations were ineffective in incorporating any of the principles related to the integrality of care, as suggested by the person-centred approach. Rather, approaches like additive sequential decision-making (Bower et al. 2011), which give precedence to pressing issues, or guidance-cooperation models (Chipidza et al. 2015) that place healthcare providers in authoritative roles, are frequently used. Additionally, the dominant pressure on healthcare providers in primary care is to meet the managerial criteria of QOF alongside clinical interviews, fails to address the comprehensive needs of individuals with multimorbidity during consultations (Turabian, 2019). This includes developing a nuanced understanding of all the biopsychosocial factors that define a patient's multimorbidity (Forslund et al. 2021), or prioritising agreed ‘master’ problems (Turabian, 2019) or an establishment of an agreed personalised care plan (Coulter et al. 2013). These are all crucial parameters for the establishment of trusted therapeutic relationships (Garg et al. 2016), ensuring furthermore the continuity and integration of care (Turabian, 2019). In summary, limited consultation time has been recognised as a major barrier to the effective delivery of care (Grag et al. 2016), resulting in a dysfunctional clinical interview and ultimately poorer health outcomes (Levenstein et al. 1986). This process is deemed unsatisfactory by people with multimorbidity, who desire a more participatory role in their healthcare, with their perspectives being respectfully and meaningfully incorporated into a tailored health delivery plan (Moody et al. 2022). However, as participants in the current study emphasised, consultations with healthcare providers often resemble a mechanistic prescription-focused process. Either way, this situation pushes the delivery of healthcare provision for people with multimorbidity further toward iatrogenesis.

In the absence of comprehensive person-centre, continuity of care emerges as the next casualty of the above healthcare reforms. The inability to consistently encounter the same healthcare provider, preferably a General Practitioner (Engamba et al. 2019), responsibility for continuity of care lying with Advanced Nurse Practitioners (Stumm et al. 2019), and implementation of a triage system for accessing primary care (Salisbury et al. 2018) present primary obstacles to people with multimorbidity receiving continuity of care. These barriers and corroborating literature also indicate the lack of relational continuity between healthcare provider and (multimorbidity) patient. This, in turn, produces a series of negative gateway effects that begin with the perpetuation of the 'collusion of anonymity,' that is translated to a lack of accountability. As a consequence of this 'collusion of anonymity,' there is a failure to achieve an early useful prognosis regarding the patient's multimorbidity, thus hindering the provision of the best possible secondary prevention care. It is evident that relational continuity is decreasing in the UK despite the advantages regarding management of multimorbidity (Engamba et al. 2019). As such, rather than fostering a healthcare relationship conducive to the development of a therapeutic alliance as advocated in the literature (Little et a. 2001; Grag et al. 2016), able to facilitate the application of an effective behavioural change interventions (Keyworth et al. 2020), in practice what was found is marked by the conflicting interests that alienate participants of the healing relationship. This perpetuates the perception of a one-sided therapeutic relationship. According to literature impaired communication between healthcare providers and people with multimorbidity (Little et a. 2001) eventually leads to eroded healthcare relationships, which is directly linked with poor health outcomes (Chipidza et al. 2015). This further verifies the high risk for iatrogenic provision of care for people with multimorbidity.

Achieving continuity of care for people with multimorbidity could also require improved coordination among various healthcare services or establishing multidisciplinary teams, both of which are strongly desired by specific population (Stumm et al. 2019; Damarell et al. 2020). Findings of the present study were not optimistic in either of these areas. Similarly to suggestions from literature (Sauvage & Ahluwalia, 2016), this study found that people with multimorbidity do not consistently experience person-centred care across different healthcare settings. This was usually dictated by time constraints, a key parameter in restricting optimal care according to the present study. Furthermore, sole

reliance on referrals and signposting without subsequent follow-up or intersectoral collaboration among healthcare providers, even for critical matters like medication management, were another noteworthy finding. This reflects the fragmented care experienced by people with multimorbidity and the escalating risk of adverse drug events compromising their safety (Mercer et al. 2016) and exacerbating the potential for iatrogenic harm in their healthcare treatment.

As suggested in literature and observed in the current study, a consequence of the aforementioned systemic failures, overburdened healthcare providers resort to biomedical single-disease protocols. This is an approach that primarily focuses on somatic symptomatology, medical diagnosis, and medication treatment, thereby medicalising the entire treatment process. It is widely acknowledged that existing guidelines fail to account for the aggregate impact of suggested treatments, and that their uncritical usage will soon lead to polypharmacy (Hughes et al. 2012) and drug-drug interaction (Dumbreck et al. 2015). This common though crucial iatrogenic consequence is thought to account for approximately 6% of unplanned hospitalisations. This conflicts with another key replicated finding here and in the literature, that individuals with multimorbidity believe in recovery and care, rather than complete cure and pharmaceutical treatment (Turabian, 2019).

By Intervening across all facets of multimorbidity care, medicalisation has essentially homogenised the entire treatment process. But homogeneity that prioritises medically related issues brings serious consequences; notably the issues of polypharmacy and shifting healthcare relationships toward prescribing medications. These are two seriously troublesome aspects related with medicalisation are currently receiving attention within the scientific community (Sinnott & Bradley, 2015; Sauvage & Ahluwalia, 2016). Additionally, participants in the current project and elsewhere expressed concern that healthcare providers have critical contributions to the emergence of both issues (Smith et al. 2010; Lawn et al. 2010; Sauvage & Ahluwalia, 2016). Both issues undermine person-centred care, risking additional iatrogenic problems such as drug adverse events and further stigmatisation of patients with multimorbidity who may not adhere to medication regimens, and become labelled as irresponsible.

On the Salutogenesis end of the spectrum, the present study highlights that SNAP-HRBs, together with the emerging profile of post-modernist patients, represent significant

counterforces to the prevailing medicalisation of multimorbidity treatment. Specifically, one major finding regarding with the emergence of the post-modern patient with multimorbidity, apart from their ability to acquire and process medical knowledge [mainly through effective usage of new technologies (Smailhodzic et. al. 2016; Qudah & Luetsch, 2019)], is the gradual decline in recent years of 'public trust' in medicine as an institution (Mechanic, 1996). This has resulted in a specific category of patients with multimorbidity who exhibit resistance to extended medication use or polypharmacy. Moreover, they tend to avoid transforming their therapeutic alliances with healthcare providers into primarily pharmaceutical interactions. Such individuals advocate for reduced reliance on medication, pursuing more comprehensive and empowering treatments that prioritise their holistic well-being as the means to attain better health outcomes (Melungeons & West, 2016).

SNAP-HRBs play a crucial role in steering multimorbidity care toward the salutogenic approach that people with multimorbidity often desire. For instance, research in polypharmacy has demonstrated that incorporating behavioural theory can effectively enhance medication management (Sinnott & Bradley, 2015). However, despite the positive inclination of people with multimorbidity toward behavioural change interventions, which contrasts with the perspectives of many healthcare providers (Keyworth et al., 2020), SNAP-HRBs are seldom integrated into standard healthcare procedures, despite their significant impact. This oversight persists, despite additional evidence from both the current study and existing literature, which suggests that advanced techniques such as Motivational Interviewing, as those found to be applied in community service settings, not only enhance the person-centred approach but also prove effective in addressing various health risk behaviours (McKenzie et al., 2018).

6.4.2 Implications for future research and recommendations

Based on the present findings, several recommendations are proposed. There is a compelling argument for integrating behaviour change theories (preventive medicine) as equal to medical approaches (curative medicine). This could fall within a unified multimorbidity-multibehaviours conceptual framework, recognising the significance of SNAP-HRBs as moderators of multimorbidity risk and management. It is essential to incorporate these factors into standardised procedures for assessing and managing

multimorbidity. Furthermore, suggestions for reforming the healthcare system towards a more salutogenic approach include tailoring care to meet the specific needs of multimorbidity patients, prioritising quality of life as a primary medical objective, and acknowledging patient expertise alongside that of medical professionals (Damarell et al. 2020). Further efforts should focus on addressing critical health concerns, implementing agreed plans based on prognostic indicators, and celebrating incremental achievements (Sauvage & Ahluwalia, 2016). On these premises, initiatives such as the CARE PLUS trial led by Professor Mercer, which extended consultation duration and emphasised relational continuity with healthcare providers while providing valuable information (Sinnott & Bradley, 2015), or the 3D study (Salisbury et al. 2018), which integrates behavioural theory through models of behaviour change, have demonstrated positive effect on patients with multimorbidity quality of life and overall well-being.

6.4.3 Conclusion

This study sought to address the gap regarding the combined impact of multimorbidity and multibehaviours on the doctor-patient healthcare relationship. The findings provide important insights into an overlooked aspect of multimorbidity literature; the importance of healing relationships in the context of multimorbidity under the construct of person-centred care. This has practical significance for the development of optimal provision of healthcare for people struggling with multimorbidity-multibehavioural issues for two reasons. Firstly, it has been convincingly argued that the person-centred approach should be developed as a 'pragmatic' solution to the complexities in multimorbidity healthcare (Kamerow, 2012). Secondly, the quality of shared responsibilities in doctor-patient relationships serves as a direct reflection of the quality of healthcare services provided to the entire patient population (Prochaska, 2008).

Therefore, there is a clear need to shift the present provision of multimorbidity's healthcare toward a novel conceptual and operational framework that integrates both the optimisation of medical interventions, and behavioural theories, particularly concerning the prominent SNAP-HRBs. The present research, echoing the suggestions of other scholars (Loprinzi, 2015), posits that a unified multimorbidity-multibehaviours framework can fulfil this role, necessitating essential systemic modifications to achieve improved person-centred care for individuals with multimorbidity.

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The Situational Analysis, which investigated the combined impact of multimorbidity and multibehaviours on the healing relationship between healthcare providers and individuals with multimorbidity, marked the culmination of the comprehensive examination of the interrelationship between multimorbidity and multibehaviours in this project. The subsequent final chapter synthesises findings from Chapters 3-6 to discuss the thesis's contributions, implications for research and practice, and the overall strengths and limitations of this work.

7. Discussion

The discussion sections within **Chapters 3-6** summarised the findings that emerged from the respective studies in the context of existing literature. This chapter presents an overarching discussion of the PhD, focusing on key issues identified through the various studies, providing a more comprehensive picture of the contributions to knowledge, the strengths and limitations, and potential implications for future research and practice.

7.1 Main findings

In **Chapter 3**, the systematic review and meta-analysis provided robust evidence of the complex interplay between multimorbidity and SNAP multibehaviours, further highlighting the significance of the operational definition used for examining multimorbidity and the special attention needed regarding the sex-specific differences that are related with the phenomenon. Specifically, the meta-analysis revealed that the association between multimorbidity and engaging in multiple SNAP-HRBs varies based on the number of SNAP-HRBs involved, as well as the operational definition of multimorbidity. As such, a positive dose-response association between the number of SNAP-HRBs and multimorbidity risk was found, not only when more SNAP-HRBs were examined under a specific operational definition of multimorbidity, but their association became stronger when the same number of SNAP multibehaviours were examined using a higher cut-off for the operational definition of multimorbidity. In addition to this above twofold dose response association, meta-analytic evidence derived from the review also identified sex-specific differences in the relationship between multimorbidity and SNAP behaviours. Men and women exhibited different thresholds for developing multimorbidity based on the number of SNAP behaviours or the definition of multimorbidity used. Specifically, men's multimorbidity risk appeared closely related with the number of SNAP-HRBs involved (i.e., two or more health risk behaviours), while women showed a significant association with multimorbidity-SNAP-HRBs only under the multimorbidity definition of MM3+. Interestingly, the systematic review and meta-analysis revealed that, although women appeared less affected by the association between multimorbidity and multibehaviours under the MM2+ definition, this trend was

reversed when considering the engagement with three SNAP-HRBs using the MM3+ definition, where the association was greater in women than in men.

The review's identification of the dose response association pattern and the sex differences regarding with the multimorbidity risk when engaging with SNAP multibehaviours warranted further examination. This prompted the epidemiological study in **Chapter4,** primarily due to the scarcity of studies examining these aspects. Pragmatically, this decision was driven by the need to enhance the existing evidence that would inform future multimorbidity guidelines. This is important as systematic reviews are regarded as the best available evidence on which to base public health practice and policy (White, 2019). **Chapter 3** highlighted that current evidence was impeded by the limited number of studies investigating the specific inquiries and methodological challenges among primary studies leading to high heterogeneity.

For that reason, the study adopted a comprehensive approach examining the effect of different combinations and accumulations of SNAP-HRBs on multimorbidity risk, considering the three major operational definitions in use (MM2+, MM3+ and Complex MM). This approach was deemed the most suitable due to the absence of a standardised method for investigating multimorbidity and to effectively address its primary objectives. Once more, a consistent finding was a positive dose-response association between SNAP-HRBs and multimorbidity: a higher number of SNAP-HRBs correlated with a greater likelihood of identifying multimorbidity. This pattern supported the notion that combined or cumulative health behaviours influence multimorbidity risk. Specifically, the epidemiologic study revealed significant outcome effects for all possible combinations of SNAP-HRBs dyads in relation to multimorbidity, challenging previous studies that reported varying associations for specific dyads of SNAP-HRBs. Despite the slight variability in the dose-response association identified with specific dyads, this was overshadowed by the consistent dose-response association effect between accumulated SNAP-HRBs and multimorbidity across different operational definitions. In essence, in line with previous research, the epidemiological study demonstrated a significant association of accumulated SNAP-HRBs with multimorbidity risk.

Regarding the second major objective, the epidemiological study observed variations in sex patterns depending on the multimorbidity definition. This suggests that sex may influence the relationship between health behaviours and multimorbidity. Indicatively,

when dyads of SNAP-HRBs examined, sex pattern identified for two multimorbidity definitions, specifically MM2+ and Complex (not MM3+). In these cases, women were found to have larger associations between SNAP-HRBs and multimorbidity. However, when analysing cumulative SNAP-HRBs, the picture was reversed: men were found to have stronger associations between SNAP-NRBs and multimorbidity across all levels of accumulative SNAP-HRBs and multimorbidity definitions.

Building on this, the second epidemiological study in **Chapter 5** provided further aetiological evidence regarding with the sex differences in multimorbidity-multibehaviours phenomenon by examining the existence of different associative multimorbidity patterns in both sexes; i.e., the identification of non-random associations between the morbidities (Prados –Torres et al. 2014) that may affect males and females differently. The study revealed eight patterns: five for males (metabolic-cardiovascular, genitourinary track disorders, respiratory and vision spectrum disorders, ocular spectrum disorders, and neurovascular – gastro-renal syndrome) and three for females (cardiometabolic and neurovascular spectrum disorders, respiratory conditions, and sensory impairments). These further verified the important effect of accumulated SNAP-HRBs to the development of, not only various specific morbidities, but distinct multimorbidity patterns, emphasising the importance of addressing them as modifiable risk factors. The revelation of clinically stable multimorbidity patterns where SNAP-HRBs could be regarded as key etiological determinants, was the central narrative of in **Chapter 5**, and among the few in this field of inquiry. To summarise, only the pattern for cardio-metabolic-vascular was common to males and females, although with noticeable differences in their manifestations. The remaining identified patterns did not match across. Besides the cardiometabolic-(neuro)vascular pattern, other multimorbidity patterns differed between males and females, highlighting sex-specific health risks and disease associations.

The final empirical study in **Chapter 6**, analysed the implications of the findings from **Chapters 3-5** in the context of the healing relationships between healthcare providers and individuals with multimorbidity. This final qualitative study moved the PhD in a practical direction, using in-depth qualitative methods and speaking to people with multimorbidity and their healthcare providers to understand how multimorbidity and SNAP-HRBs are considered in routine care. This allowed the thesis to transition towards

evidence-based practical recommendations. This applies to both assessment and treatment processes for managing or addressing the progression of multimorbidity. These findings also shed light on the challenges of self-management faced by individuals with multimorbidity, including medication-related concerns, time constraints, and communication issues with healthcare providers as crucial barriers to implemented necessary SNAP-HRBs changes for multimorbidity management. Moreover, if health professionals overlook these challenges, this can lead to unintentional assumptions about patients' motivation and responsibility for self-care, an issue that the systematic review meta-analysis (**Chapter 3**) clarified. This supported the case to move away from the notion of "personal responsibility," which asserts that individuals are solely responsible for the consequences of their perceived unhealthy lifestyle "choices," thereby carrying the entire burden of their own health (Minkler, 1999). This oversight can result in stigmatisation and feelings of being judged among patients with multimorbidity, further alienating them from the healthcare system. Similar to healthcare providers overlooking SNAP-HRBs, sex differences were rarely mentioned as part of treatment processes within the provision mainstream healthcare. On the contrary such issues emerged from healthcare providers who activate themselves outside the mainstream healthcare. Such healthcare providers are more prone to provide person centred approaches, like Motivational Interviewing, as ways to support people with multimorbidity toward behaviour change (in SNAP-HRBs). In summary, **Chapter 6** underscored the importance of person-centred care in managing the complexities associated with multimorbidity-multibehaviours. Employing a Situational Analysis methodology, the pragmatic nature of the present thesis took a more post-modern interpretative turn regarding the multimorbidity-multibehaviours issue. Findings emerged via a theoretical sampling in action process, suggested the conceptual framework of Salutogenesis and Iatrogenesis dipole. This framework highlights the risks posed by medicalisation and manipulation of time in healthcare settings, while also emphasising the role of SNAP-HRBs as countermeasure in promoting holistic health approaches. It also helped to develop evidence-based recommendations considered in section 6.4.

7.2 Agreements and Disagreements with Other Studies

The evidence of positive dose-response association between multimorbidity and SNAP multibehaviours identified from Systematic Review meta-analysis in **Chapter 3**, not only aligned with previous research that examined the association between single SNAP-HRBs and multimorbidity (Cao et al. 2019; Jackson et al., 2016; Mohd et al. 2019; Wikstrom et al. 2015) but it complements their evidence by demonstrating a positive dose response associations analogous to the number of SNAP-HRBs involved and the operational definition of multimorbidity used. This evidence is further supported by a modern study published outside the time range of completion of the systematic review meta-analysis, which shows again a strong association between certain clusters of SNAP -HRBs and specific multimorbidity patterns in the older England population (Suhag et al. 2024).

Furthermore, by examining the combined effect of multiple behaviours and how the MM-SNAP-HRBs association varied by sex and multimorbidity definition, it shed light on the well-known phenomenon in multimorbidity literature of sex differences. Indicatively, while existing literature acknowledges sex differences in multimorbidity prevalence, with a higher prevalence trend for women than men at all ages (Agur et al., 2016; Adad-Diaez et al., 2014; Afshar et al., 2015), this review provided deeper insights into how these differences manifest in the context of multiple behaviours and multimorbidity definitions.

Both findings confirmed and augmented by the epidemiological study in **Chapter 4**, demonstrated that all form of multiple SNAP-HRBs significantly intervene in the risk of multimorbidity for both sexes regardless of its operational definition. Such findings, however, contrast with some previous research, which reported different associations between specific SNAP-HRBs and multimorbidity risk for males and females (Fortin et al., 2014), specifically when the interest of investigation targeted on SNAP-HRBs dyads (Loprinzi, 2015). This variability may stem from differences in study populations, methodologies, and multimorbidity operational definition used.

Following **Chapter 4**, which focused on identifying clinically valuable patterns able to inform future guidelines around combinations of SNAP-HRBs that increase the risk of multimorbidity; **Chapter 5** revealed sex patterns of associative multimorbidity-multibehaviours where direct comparison with other studies is challenging due to the

heterogeneity in study designs, populations, included morbidities, and analytical methods. Specifically, unlike other studies that focused on older adults, this study included a broader age range to increase clinical value. It used primary care electronic health records (EHRs) and employed exploratory factor analysis (EFA) as the main analytical method. However, despite this heterogeneity, some patterns identified in this study resemble those in previous research (Prados-Torres et al. 2012; Abad-Díez et al. 2014). The cardiometabolic-vascular pattern was consistently observed in various studies, as were respiratory patterns (Jackson et al. 2016). Additionally, the genitourinary tract disorders pattern in males resembled patterns found in other studies focusing on gastrointestinal and cancer patterns (Kirchberger et al. 2012).

The final empirical study in **Chapter 6** was the first study to use Situational Analysis to examine the joint impact of multimorbidity-multibehaviours interplay on the healing relationship between the healthcare providers and patients with multimorbidity. Despite theoretical principles advocating for person-cantered care (Sauvage & Ahluwalia, 2016; Mercer et al. 2016), the study identifies significant gaps in its practical application, particularly in the context of multimorbidity care. Existed disparities furthermore, between theoretical principles and real-world practices, prevent the transition toward a more salutogenic approach where the inclusion of SNAP-HRBs as standardised procedure of assessing and treating people with multimorbidity will be normality rather than exception (Loprinzi, 2015). Nevertheless, study findings which showed that fundamental person-centred principles such as Integrality (Levenstein et al. 1986; Turabian, 2019), relational continuity (Engamba et al. 2019), and integrated provision of care (Damarell et al. 2020) found to be often overlooked in clinical settings, resulting in ineffective consultations and poorer health outcomes for individuals with multimorbidity aligned with concerns posed by other studies on the field of person-centred care and multimorbidity management (Bower et al., 2011; Valderas et al., 2010). Prominent among those studies whose findings accord with those in **Chapter 6** is s the work by Lawn et al. (2010), which investigates how healthcare systems categorize individuals with chronic conditions as responsible self-managers. This idea is in total contrast not only with the qualitative findings emerge from **Chapter 6** but furthermore the evidence derived from the systematic review meta-analysis in **Chapter 3**.

7.3 Contribution to literature

The findings presented in this thesis significantly contribute to the existing knowledge by expanding on the recommendations put forth by Loprinzi (2015) regarding the necessity of establishing a unified framework for multimorbidity and multibehaviours. Overall, this PhD contributes the first pragmatic exploration of how such a framework could be constructed, bridging the gap between curative and preventive medicine (Prochaska, 2008) for people with multimorbidity and SNAP multibehaviours. To accomplish this overarching goal, several smaller-scale contributions to the literature were achieved.

Specific contributions to knowledge are summarised.

1. The systematic review meta-analysis (**Chapter 3**) was the first to explore the interrelationship between of multimorbidity and multibehaviours. It furthers our knowledge by quantifying their interrelationship, showing the strong positive dose response associations between SNAP multibehaviours and multimorbidity, and suggesting the turn of the focus of the scientific inquiry toward the multifaceted nature of phenomena such as health risk behaviours (Prochaska, 2008) and morbidities (Van den Akker et al. 2001). Furthermore, it underscores the importance of conducting multidisciplinary research for informing health policy frameworks, which traditionally prioritise the treatment of individual diseases (Shadmi, 2013).

2. The epidemiological studies provided novel evidence to help shape future guidelines, responding to the call of researchers such as McKenzie et al., (2018), to equally attribute importance to SNAP-HRBs as to pharmaceutical treatment within future guidelines for people with multimorbidity. Specifically, the first epidemiological study (**Chapter 4**) addressed a significant gap in the literature by examining the combined and cumulative effects of SNAP-HRBs on both simple count (MM2+, MM3+) operational definitions of multimorbidity and the cumulative index of Complex multimorbidity. This study responded to the call for more conclusive etiological evidence on these factors (Violan et al. 2014). The findings complement existing studies by demonstrating positive dose-response associations of all SNAP-HRBs with all types of multimorbidity definitions for both sexes. An additional novelty of the study was that it was the first epidemiological investigation to specifically examine the interrelation of

multimorbidity and SNAP-HRBs on the newly emerged operational definition of Complex Multimorbidity, an area not extensively documented in previous literature.

3. The second epidemiological study (**Chapter 5**) was the first to identify specific patterns of associative multimorbidity in individuals who developed multimorbidity while engaging in SNAP multibehaviours (confirmed by electronic health records), rather than focusing on generic multimorbidity patterns in the general population. This unique approach contributes significantly to current knowledge by providing evidence of the existence of specific patterns of multimorbidity-multibehavior associations.

4. Finally, this PhD presents the first examination of the interrelationship of multimorbidity-multibehaviours in the context of mainstream healthcare delivery (**Chapter 6**). This provided valuable insights into an overlooked aspect of multimorbidity literature: the importance of healing relationships in the context of multimorbidity under the construct of person-centred care. Critically, through novel application of the Situational Analysis methodology, the major contribution was the proposal of a new conceptual framework based on Salutogenesis – Iatrogenesis dipole. This is capable of integrating both the optimisation of medical interventions and behavioural theories, especially regarding the prominent SNAP-HRBs. The researcher, echoing the suggestions of other scholars (Loprinzi, 2015), argue that a unified multimorbidity-multibehaviours framework can fulfil this role, necessitating essential systemic modifications (Dale & Lee, 2016) to achieve improved person-centred care for individuals with multimorbidity.

7.4 Implications

Findings that emerged throughout the thesis have several implications for future research and healthcare reform. The central point, however, underscores the need for future research to focus on better integration of behavioural change theories into multimorbidity care, aiming to support a twofold outcome. Firstly, this integration is expected to better meet the clinical needs of people with multimorbidity. Secondly, it is anticipated to facilitate healthcare system change towards a salutogenic approach, that effectively balanced patients' needs for both "cure" and "care" within mainstream healthcare settings.

Specifically, the first part of the thesis examined how the accumulation of SNAP-HRBs contributed to development of multimorbidity. While in the second part of the project,

Situational Analysis provided a more integrated perspective by exploring the combined impact of multimorbidity-multibehaviours on the diagnosis and prognosis of people receiving multimorbidity care.

7.4.1 Implications for research

Implications for future research emerge from the findings in the two research **Chapters 4** and **5** which encompass both clinical-epidemiological and behavioural-change inquiries.

There is a need for further examination of the identified dose-response association concerning issues related to the current project. This may include further clarification of the identified interchangeable sex patterns, and whether these patterns associated with different accumulations of SNAP-HRBs, the multimorbidity operational used, their combinations or based on other unidentified reasons.

Further research implications that arise from the identified dose-response association could expand the scope of the current project. For instance, although not meta-analytically examined, evidence derived from the Systematic review (**Chapter 3**) suggested that SNAP-HRBs can account for approximately 40% of the social patterning of multimorbidity (Katikireddi et al., 2017). This is a significant proportion but leaves enough yet to be explained. This underscores the importance of further investigating the potential dose-response impact of SNAP-HRBs in reducing health inequalities in comparison to other wider determinants of health (e.g., housing) which current evidence has shown are of equal significance to multimorbidity risk (DHSC, 2023).

Further investigation of the cumulative impact of SNAP-HRBs on associative multimorbidity examining emerging patterns is essential. For example, the sex differences observed via the identification of distinct patterns of associative multimorbidity-multibehaviours in **Chapter 5** clearly suggest the need for further investigation into possible different determinants or magnitudes of effect. In essence, future research should focus on issues related with the understanding of the shared aetiology between SNAP-HRBs and multimorbidity in generating specific sex patterns, in the possibility that this research will uncover novel associations and pathways contributing to multimorbidity risk. In conclusion, inquiries into both dose response

association and sex patterns in associative multimorbidity could address a gap in research knowledge, informing future clinical guidelines and research.

On an interdisciplinary level, the evidence of a dose response association here aligns with the recently emerged inquiry in behavioural theory regarding with the multiple health behavioural change interventions. As such, rather than debating the effectiveness of single or multiple health behavioural change interventions, research should prioritise the identification of the most impactful approaches of multiple health behavioural change interventions within the framework of multimorbidity and multibehaviours. For example, among other things, a key question that needs to be answered is whether sequential (addressing one HRB at a time) or simultaneous (addressing all HRBs together) approach is a more effective (Prochaska, Spring, Nigg, 2008).

On a methodological level, the systematic review meta-analysis has revealed through the implementation of a subgroup analysis that a possible source of heterogeneity was methodological mismatch with the proposed threshold of 12CC (Fortin et al. 2012). As shown, multimorbidity studies that involved fewer than 12 morbidities produced significantly different associations, between multimorbidity and SNAP multibehaviours, compared with those from studies that examined the recommended threshold of ≥12CC. The implication for further studies on identifying a “golden standard” measurement as an operational definition of multimorbidity is of utmost importance, not only theoretically, but also on a practical level, due to its significance in policymaking and the development of tailored interventions. However, the introduction of the “experiential” definition from Blarikom et al. (2023) offers a pragmatic solution.

Finally, future research could explore linking the emerging idea of the Salutogenesis-Iatrogenesis dipole with other similar concepts, such as the House of Care project (REF), which also centralises Salutogenesis as the driving force of the healthcare system, but from a systemic theory perspective. Such integration between the two projects could provide evidence not only on systemic failures, but more crucially, on developing balancing feedback loops that would better support patients in their efforts to increase their quality of life while simultaneously managing multimorbidity.

7.4.2 Implications for practice and healthcare systems

Several practical implications arise from the present findings but perhaps aligning theory with practice is most crucial for addressing the challenges posed by SNAP multibehaviours and multimorbidity.

7.4.2.1 Healthcare providers

Healthcare providers could benefit from training to implement multiple health behavioural change theory aspects as part of their secondary prevention care. A good practical example is training of mainstream healthcare providers to advance interview techniques like Motivational Interviewing, that have shown promise in addressing health risk behaviours associated with multimorbidity. This could enhance the person-centred approach and lead to improved patient outcomes.

Furthermore, training healthcare providers on the theoretical construct of salutogenesis and consultation techniques like review dialogues could enhance their ability to adopt a more holistic approach when working with people with multimorbidity, build stronger therapeutic alliances by promoting comprehensible, manageable and meaningful treatment approaches by recognising and navigating more effectively their patients' on their health challenges, thereby optimising their engagement with health-promoting behaviours (Rojatz et al. 2022).

Finally, future guidelines on multimorbidity stand to benefit from integrating the findings of the present project concerning the evidence of dose-response association and sex patterning. This further supports those advocating for the development of multimorbidity guidelines that embrace a more person-centred approach, encompassing behavioural factors pertinent to individuals with multimorbidity.

7.4.2.2 Healthcare systems

Following Prochaska's (2008) suggestion regarding the breakdown of disciplinary silos with simultaneous fostering of interdisciplinary collaboration, the present project aimed to synthesise evidence from both curative and preventive medicine disciplines to suggest a pragmatic approach to reforming the current monomorbid healthcare system. The newly developed Integrated care systems in the UK will be benefit from such

interdisciplinarity that will enable clinicians and researchers to develop a better understanding of the complex interrelations between multimorbidity and multibehaviours, moving their theoretical conceptualisations and clinical practice towards a better applied person-centred approach, such as the notion of salutogenesis, as it regards the management and secondary prevention care of patients with multimorbidity-multibehaviours.

This paradigm shift must prioritise the healing relationship between healthcare providers and patients (people with multimorbidity), moving towards the metaphor of a therapeutic alliance. A crucial aspect of this process is the ability to scrutinise whether the delivery of person-centred care meets the needs of people with multimorbidity.

Within this context of providing multimorbidity care, the complexity uncovered through Situational Analysis emphasises the need for a holistic approach that surpasses the traditional focus on single diseases. Integrating preventive and curative medicine into a unified conceptual framework of multimorbidity-multibehaviours, as proposed by the Salutogenesis-Iatrogenesis dipole, can lead to more effective and person-centred care.

The adoption of the salutogenic perspective by Integrated Care Systems (ICS) in the UK, as a counterpoint to the current disease-focused iatrogenic implementation of healthcare demands a fundamental redefinition of health that emphasises integrality and comprehensiveness of care away from disease diagnostics. This perspective aims to provide individuals with multimorbidity a greater sense of coherence about their situation, providing an overarching health construct for managing the complexities surrounding their conditions.

Central to this approach is the development of trusting, healing relationships between healthcare providers and individuals with multimorbidity, that move beyond personal responsibility and the notion of the (ir)responsible self-managing patient, to enhance relational continuity, Integrality of care, and better integration of healthcare services.

Health promotion and delivery is focused on adopting salutary health-enhancing factors/behaviours rather than how one's will avoid the health-pathogens. Thus, the immediate effect from this redirection of healthcare delivery will be better adoption of sense of coherence from people with multimorbidity. Moreover, by targeting health literacy, a key target of salutogenic approach, healthcare providers are transformed from

what is currently seen as an authoritarian figure and leadership, to a partner in a therapeutic alliance that acknowledge patient's expertise and contribution.

Assessment and advice or sequential decision models will be replaced by techniques like review dialogue that better align with pace and time needs of people with multimorbidity. Through these techniques healthcare providers will be able to empower people with multimorbidity to co-produce a treatment plan the will respect the patient's wishes, attitudes etc. Nevertheless, the primary objective of the consultation process will be the patients' acquisition of positive feelings that will lead them to the comprehensibility, manageability, and meaningfulness (via participation) of their situation (Bauer et al. 2020). Evidence has shown that a strong therapeutic alliance between healthcare providers and patients is essential for improving self-management, particularly for people with multimorbidity (Corso et al. 2012; Baxter et al. 2018).

It is essential that this process takes place within primary care settings and is guided by a GP practitioner, a role that evidence suggests is preferred by individuals with multimorbidity.

The inclusion of behavioural change scientists as participatory members of multidisciplinary teams can contribute further to this as well as to the establishment of salutogenic reform of the newly emerged integrated care systems. This study's evidence strongly supports Dale & Lee's (2016) model. This acknowledges the importance for participants people with multimorbidity of having a healthcare role able to be responsible and accountable for the psychological and behavioural aspects attached to managing multimorbidity. As such, encouraging integrated care systems on the direction of integrating social workers, psychologists and accredited behavioural scientists as part of primary care multidisciplinary teams, is highly recommended.

Finally, salutogenesis extends beyond individual health to encompass the social and community dimensions of well-being. It emphasises the availability and accessibility of generalized resistance resources such as social support, education, and healthcare services, which individuals, including people with multimorbidity, can utilise to enhance their ability to manage health challenges effectively. Despite some criticism, social prescribing can play a key role in this process by connecting individuals to available services that align with shared values of positive health and well-being. Rather than

merely promoting lifestyle changes, this approach facilitates access to meaningful and manageable resources, empowering individuals to address health inequalities and enhance their overall sense of coherence.

In summary, adoption of salutogenesis by the newly emerging integrated care systems in England would be beneficial, from its reforming power of salutogenic approaches toward the strengthening of therapeutic alliances and the integration of morally determined social prescribing practices, that are currently lacking from the healthcare system for people with multimorbidity.

7.5 Strengths and limitations

The project had various several strengths and limitations, which are summarised for each study.

In **Chapter 3**, the strengths of the systematic review included a predefined protocol and a comprehensive analysis of various multimorbidity-SNAP relationships, able to secure an internal validity to the study's main results regarding with the identification of the dose-response associations between SNAP behaviours and multimorbidity risk, and the differential sex patterns. Limitations related to the high heterogeneity in pool effects despite being resolved via subgroup analysis. Nevertheless, high heterogeneity suggests that caution is required regarding the interpretation and generalisability of results. It was also not possible to duplicate all stages of the review (i.e. two researchers independently screening all titles/abstracts), given the limited resources available that attached with the fulfilling requirements of the PhD thesis. Finally, the lack of examining grey literature, due to limitations posed by PhD time limits, is another limitation that may also linked with possible publication bias.

In **Chapter 4**, study strengths included the large sample size, use of electronic health records to enhance accuracy of morbidity data extraction and multiple imputation techniques to address missing data, which strengthened the statistical power and generalisability of study's findings. The implementation of a comprehensive multimorbidity index that met the recommended threshold of 12 chronic conditions, further strengthened the validity and reliability of multimorbidity assessment. Limitations related to the cross-sectional study design, which limits the ability to

establish causal relationships or investigate the temporal sequences between SNAP-HRBs and multimorbidity development. There were also weaknesses from the HRB recording in primary care records. As detailed in section 4.2.4 and Appendices 10-13, these issues were mitigated as far as possible, but the influence of variable recording of health behaviours (in quality and completeness) is acknowledged. Furthermore, despite all the efforts implemented by the Ph.D. researcher and the expert personnel from the CSU to address possible double counting in electronic health records, this threat could not be entirely excluded. Finally, the convenience sample of three participating General Practices, despite covering the necessary variation of the examined group, may pose a threat to several biases, such as selection bias, and confounding variables, such as frequency of GP visits and practice variability, especially in EHR completeness, GP prescribing behaviours, even possible difference and/or omissions regarding the diagnostic coding of morbidities.

In **Chapter 5**, again, large sample size, inclusion of numerous morbidities, and the use of electronic health records for high-quality data extraction are strengths. Moreover, factorial analysis provided a rigorous analytical approach, allowing for the interaction of morbidities and the identification of clinically valuable patterns minimising confounding influences. High prevalence of included morbidities and adequate goodness of fit measures further support the reliability of the findings. Limitations of this study include incomplete morbidity coverage (e.g., obesity that may have impacted to the lack of the identification of certain patterns) and exclusion of people without multimorbidity from the analysis may overestimate correlations between morbidities, biasing the correlation matrix. Finally, the aforementioned limitations in recording of lifestyle behaviours in primary care data may have led to under- or over-representation of certain conditions.

In **Chapter 6**, use of Situational Analysis is among the strengths of present PhD thesis overall. The iterative process, development of the three conceptual cartographic maps and the implementation of the theoretical sampling in action process guaranteed the grounded effect of the methodology. The benefits and strengths of the methodology are detailed in section 6.4.2. However, this study was limited by the relatively small number of interviews and its reliance on a convenience sample of material used for the desk-based research part, a constraint imposed by the time and resource limitations of the PhD, which could have affected the saturation of the study.

7.6 Conclusion

This research project was a novel investigation regarding the complex interrelationship of multimorbidity and multibehaviours, and their combined impact on the current mainstream healthcare system, which combined a series of robust and distinct quantitative and qualitative methodologies. By scrutinising this overlooked area, the present thesis not only revealed the importance of accumulative SNAP-HRBs in the development of multimorbidity through a dose-response association but also is illuminates how this process differs between sexes, resulting in distinct patterns of associative multimorbidity. These findings drove the further investigation of how the collective influence of various health phenomena, such as multimorbidity-multibehaviours, shapes the healing relationship between healthcare providers and individuals with multimorbidity. Thus, it enhances our understanding of how to provide more equitable and effective healthcare services to this specific population, within the context of person-centred healthcare.

While acknowledging its limitations, the project emphasises the need for a paradigm shift in healthcare towards a holistic approach that encompasses both preventive and curative medicine constructs and practices, both in the prevention and management of multimorbidity. At the core of this project lay the belief that prioritising person-centred care, fostering interdisciplinary collaboration, and introducing the joint framework of multimorbidity-multibehaviours in both research and clinical practice can support healthcare system's provision of care to better address the complex needs of people with multimorbidity.

It is believed that adopting such an approach could ultimately result in improved health outcomes and quality of care, mitigating the observed discrepancy between theory and practice within the mainstream healthcare system. By employing a Situational Analysis on the current provision of healthcare of people with multimorbidity, the present project unveiled the conceptual framework of Salutogenesis-Iatrogenesis dipole to support this goal. This framework highlights the risks associated with medicalisation and manipulation of time in healthcare settings, while also emphasises the role of countermeasures like SNAP-HRBs and therapeutic alliances in promoting holistic health approaches leading to better integrality, continuity, and integration of care for people with multimorbidity.

In conclusion, moving forward, efforts to reform the healthcare system should prioritise person-centred approaches that will incorporate strategies that effectively address multiple health risk behaviours based on emerging evidence from interdisciplinary research within a unified conceptual framework of multimorbidity and multibehaviours.

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