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# Predictors of frailty and multimorbidity in adults aged 40 to 65 years in a rural population cohort in Burkina Faso

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**UNIVERSITY OF THE WITWATERSRAND**

**FACULTY OF HEALTH SCIENCES**

**SCHOOL OF PUBLIC HEALTH**

# PREDICTORS OF FRAILTY AND MULTIMORBIDITY IN ADULTS AGED 40 TO 65 YEARS IN A RURAL POPULATION COHORT IN BURKINA FASO

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**A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Science in Epidemiology in the field of Epidemiology and Biostatistics**

**Johannesburg, 2024**

**January, 2024**

## DECLARATION

I Georges Somé declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

**Signature** 

**Date: 10th day of January 2024 in Johannesburg**

# DEDICATION

**To Almighty God**

For blessing my efforts and giving me the strength, hope and energy to accomplish this work. Nothing would have been possible without your will.

**To my parents in memory**

You had blessed us; you had forged in us a taste for a job well done and you had always taught us to give the best of ourselves and to persevere in the effort. Peace and Mercy for your souls!

**To my uncle Edilbert Somé**

You have always supported me during all these years, to the extent of your means. I dedicate this work to you, the fruit of the many sacrifices made for my education; find a source of pride and honour towards you. May God keep you long!

**To my beloved Teworinouor Honorine Somda**

For your constant love and support, I thank God for allowing us to meet. May our relationship grow and mature under the shadow of his grace and with the will of providence.

**To my brothers and sisters**

Each of the pages of this work carries your imprints. You have been invaluable during my difficult times. May this work inspire you and serve as a springboard! All my gratitude and brotherly love!

# ABSTRACT

**Background**: Frailty and multimorbidity are vulnerable geriatric syndromes that pose a disability problem among the elderly in Sub-Saharan Africa (SSA). Assessment of factors associated with frailty and multimorbidity in middle-aged adults has remained limited despite the prevalence established in previous studies. We determined factors associated with frailty and multimorbidity among middle-aged adults in rural areas from 2015 to 2022 in Burkina Faso.

**Methods**: This study utilized data from the Africa Wits-INDEPTH Partnership for Genomic Research (AWI-Gen) sub-study, a retrospective cohort study of 1500 participants aged 40-65 residing in Nanoro and Yako in Burkina Faso between 2015-2022. Each participant was asked to complete a standardized and structured questionnaire on socio-demographic, lifestyle, and clinical information. In addition, measures of Fried's phenotypic frailty components, and twelve chronic diseases were assessed for derivation into frailty and multimorbidity score variants respectively. To determine the risk factors associated with frailty and multimorbidity, we performed an ordinal and multinomial logistic regression analysis respectively with a significance level of 5%.

**Results**: The prevalence of pre-frailty and frailty was 59.3% and 8.5% respectively while that of multimorbidity was 38.3%, where the multimorbidity prevalence rate stratified by existing chronic diseases was 13.0%. Half of the participants who had multimorbidity were frail (47.2%) while 10.4% of frail participants had multimorbidity. Weight loss (23.9%) and self-reported exhaustion (23.1%) were the most frequent phenotypic components. Dyslipidemia (63.9%), hypertension (26.4%) and rheumatic arthritis (15.0%) were the most frequent chronic diseases. On the one hand, age (≥50 years, aOR 1.4[1.0-1.9]), being widowed (aOR 1.5[1.1-2.1]), being unemployed (aOR 2.5[1.1-5.8]), smokeless tobacco use (aOR 2.5[1.1-5.7]), being underweight (aOR 26.2[17.1-40.2]) and multimorbidity (aOR 1.4[1.0-2.1]) were independently associated with increased odds of frailty. However, fruits (aOR 0.9[0.8-1.0]) and vegetables consumption (aOR 0.9[0.8-1.0]), and being highly active in weekly activities (aOR 0.1[0.0-0.2]) significantly reduced the odds of frailty. On the other hand, age (≥60 years, RRR 1.8[1.1-2.8]), being a woman (RRR 2.6[1.7-3.9]), being widowed (RRR 1.6[1.0-2.7]), being unemployed (RRR 4.5[1.1-18.0]), overweight (RRR 5.0[2.8-9.1]), obesity (RRR 3.4[1.1-11.0]), pre-frailty (RRR 1.8[1.2-2.6]) and frailty (RRR 2.1[1.0-4.2]) were strongly associated with an increased risk of multimorbidity. Nevertheless, the consumption of alcohol (RRR 0.4[0.3-0.6]) and fruit (RRR 0.9[0.8-1.0]) significantly reduced the risk of multimorbidity. There was no significant association with determinants such as gender, level of education, smoking status.

**Conclusion**: These findings provide additional evidence on the determinants of frailty and multimorbidity in Burkina Faso. Community awareness initiatives should be strengthened to influence lifestyle on tobacco consumption, alcoholism, physical activity, and vitamin supplementation associated with the consumption of fruits and vegetables.



**Keywords**: Frailty phenotype, Multimorbidity, Middle-aged adults, Risk factors, AWI-Gen, rural Burkina Faso, Sub-Sahara Africa.

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## LIST OF ABBREVIATIONS / NOMENCLATURE

**AWI-Gen** : Africa Wits-INDEPTH Partnership for Genomic Research

**BMI** : body mass index

**CD** : chronic disease

**CES-D** : Center for Epidemiologic Studies - Depression

**CKD** : chronic kidney disease

**CKD-EPI** : chronic kidney disease Epidemiology Equation

**COPD** : chronic obstructive pulmonary disease

**CRUN** : Clinical Research Unit of Nanoro

**CVD** : cardiovascular disease

**DBP** : diastolic blood pressure

**eGFR** : estimated glomerular filtration rate

**GPAQ**: : Global Physical Activity Questionnaire

**HDL-C** : high-density lipoprotein cholesterol

**HDSS** : Health and Demographic Surveillance System

**HICs** : High-income countries

**HIV** : human immunodeficiency virus

**IQR** : interval inter-quarter range

**LDL-C** : low-density lipoprotein cholesterol

**LMICs** : low- and middle-income countries

**MLTC** : multiple long-term condition

**MVPA** : moderate-to-vigorous intensity physical activity

**NCDs** : non-communicable diseases

**OR** : odds ratio

**RRR** : relative risk ratios

**SBP** : systolic blood pressure

**SSA** : Sub-Saharan Africa

**TC** : total cholesterol

**TG** : triglycerides

**VO2max** : maximum oxygen consumption

**WHO** : World Health Organization

# CHAPTER 1: INTRODUCTION

## 1.1. BACKGROUND

The increase in life expectancy over the past decade has contributed to the demographics of aging population, so much so that geriatric syndromes are frequently observed in the elderly (1–3). Frailty and multimorbidity are vulnerable geriatric syndromes that pose a problem in older people in low- and middle-income countries (LMICs) (4–6)**.** There is a consensual disparity on the operational definitions and assessment methods of these two concepts (4,6–8)**.** On the one hand, the practical definition proposed by Fried, widely used in epidemiological studies, identifies five phenotypic criteria including: muscle weakness, exhaustion, slow walking, physical inactivity, and unintentional weight loss. The combination of 1 to 2 criteria and at least 3 criteria respectively define pre-frailty and frailty (9)**.** On the other hand, the concept of multimorbidity is defined by the coexistence of at least two multiple long-term condition (MLTC) (5,6) **.**

According to the World Health Organization (WHO), the estimate of people aged over 60 will experience a double growth of 12% to 22% between 2015 and 2050 (2). In addition to the burden of infectious and tropical diseases, Sub-Saharan Africa (SSA) faces a growing threat from non-communicable diseases (NCDs) (10,11). Indeed, the burden of NCDs increased by 67% from 1990 to 2017 (10). Similarly, WHO estimated that 77% (17 million) of deaths that occurred in LMICs were due to NCDs in 2022 (10,11). Of major importance in public health, frailty and multimorbidity are problems of international scope (4–6). Indeed, globally, the overall prevalence of frailty varies between 4.9 and 65.2% (12,13) and that of multimorbidity varies between 18 and 90% (14–16). In SSA, the pooled prevalence of frailty in community-dwelling older people varies between 4.9 and 10.6% (13) and that of multimorbidity between 35.0 and 47.2% (16–18). Over the last ten years in SSA, the prevalence of frailty, and multimorbidity varied significantly from 10.6 to 37.0% (13,19,20) and from 20 to 50% respectively from 2010 to 2020 (16–18). The prevalence of frailty in South Africa varies between 5,4-13,2% (21,22) and that of multimorbidity varies between 20,7-70,9% (18,23–25); while in Burkina Faso frailty represents 7% and multimorbidity varies between 22,8-65% (26–28)**.** Located in the heart of West Africa, Burkina Faso has a population of 21 million people with a life expectancy of 62 years (29,30)**.** The elderly represents 16% of the population (30). However, the assessment of factors associated with frailty, and multimorbidity in adults has remained limited despite the prevalence established in studies.

Evidence for the distribution of prevalence and incidence of frailty, and multimorbidity has been widely established in numerous studies (31,32). In addition, evidence on the assessment of frailty, and multimorbidity risk factors has been documented on socio-demographic factors and lifestyle factors (9,26,33–36). The evaluation of socio-demographic factors was reported on age, gender, ethnicity, level of education, marital and employment status (9,26,33,37)**.** For lifestyle factors, smoking status, smokeless tobacco use, consumption of alcohol, fruits and vegetables, and physical activities have been reported as risk factors (33–36,38). Similarly, evidence on the clinical and biological factors has been established (18,34,39,40). The association between frailty and multimorbidity has been reported with an odds ratio varying between 1.97 and 2.62 (34,41,42). This indicates that the odds of developing frailty in people with multimorbidity range from 97% to 162% higher.

## 1.2. PROBLEM STATEMENT

In SSA, most longitudinal studies have been conducted in countries such as South Africa, Tanzania, and Ethiopia (18,21,43). NCDs have been widely reported while frailty studies have been reported in nine SSA countries and multimorbidity studies in ten SSA countries from 1998 to 2022 (18,21,43). Therefore, there are few longitudinal studies on risk factors in SSA and a large disparity in estimates of frailty, and multimorbidity probably due to the population studied. The circumscription of the study population remained divergent from the point of view of the inclusion of a population that is sometimes very young and sometimes very old (28,35). Similarly, the heterogeneity of the data is mainly based on cross-sectional studies, while the progression of frailty, and multimorbidity in SSA remains under-documented (8,44)**.** The risk assessment of multimorbidity remained uncertain and inconclusive in contributing to the development of frailty or vice versa (42).

In Burkina Faso, epidemiological data on frailty, and multimorbidity over the past ten years are under-documented. Indeed, evidence on factors such as education; socio-economic status; substance use, obesity and chronic disease remain under-documented (26–28). The rare descriptive studies have been cross-sectional studies focused on a non-in-depth evaluation of frailty, and multimorbidity (26–28)**.** The proportions of some studies conducted in South Africa and Burkina Faso vary from 8.0 to 13.2% frailty (21,26) and 19 to 70% multimorbidity (18,25,27)**.** The estimate of these proportions varies according to the urban or rural study setting.

## 1.3. JUSTIFICATION

Few studies attempt to identify the predictors of frailty, and multimorbidity in middle-aged adults (40 - 65 years) in SSA, particularly in Burkina Faso (26–28). The assessment of risk factors for the occurrence of frailty combined with multimorbidity remains under-documented (42). In some longitudinal analyses, the risk assessment has remained uncertain and inconclusive, while some attempt to support the hypothesis that frailty is a prognostic factor for predisposition to multimorbidity or vice versa (42,44,45)**.** The association of socio-demographic factors, lifestyle factors, clinical and biological factors of chronic communicable and NCDs contribute to the development of frailty, and multimorbidity that can accelerate premature aging (46,47).

An analysis of the association of the effect of the various risk factors over a period of progression seems relevant. Similarly, the assessment of risk factors for the occurrence of frailty combined with multimorbidity appears relevant. Moreover, the absence of descriptive statistics coupled with the absence of pilot studies on the identification of risk factors and the incidence, influencing frailty and multimorbidity, call into question the need for the development of epidemiological monitoring of the incidence associated with the risk factors. It also challenges the characterization of the two-way relationship between frailty and multimorbidity. the predisposing factors of frailty combined with multimorbidity deserve to be explored to limit the risks of accelerated aging. The study of frailty, and multimorbidity will help to determine the incidence of these conditions; it will offer the possibility of preventing dependence in older adults and will help to characterize health states in depth while identifying those susceptible to a continual deterioration in their state of health.

## 1.4. RESEARCH QUESTION

What are the risk factors associated with the occurrence of frailty and multimorbidity in middle-aged adults (40 - 65 years old) in rural setting in Burkina Faso over the period 2015-2022?

## 1.5. AIM AND OBJECTIVES

The present study aims to determine the risk factors associated with the occurrence of frailty and multimorbidity among middle-aged adults aged 40 to 65 years in a cohort of the rural population of Burkina Faso during the period 2015-2022. Specifically, it is to:

1. Describe the distribution of attitudes about substance use, eating habits, physical activities and other behaviors associated with the occurrence of frailty in adults aged 40-65;

2. Describe the distribution of multimorbidity and associated cardio-metabolic factors in a rural population after 5 years of follow-up;
3. Identify the predictors of frailty in adults aged 40-65 after five years of follow-up;
4. Identify the predictors of multimorbidity in adults aged 40-65 after five years of follow-up

# CHAPTER 2: LITERATURE REVIEW

This section summarizes the current state of knowledge on frailty and multimorbidity. It makes the case of the various studies centered on the epidemiological distribution of frailty and multimorbidity at the global level and in SSA more particularly in South Africa and Burkina Faso. Current knowledge on socio-demographic, lifestyle, and medical-clinical factors associated with frailty and multimorbidity have been reported in this chapter.

## 2.1. HISTORIES, CONCEPTS, DEFINITIONS OF FRAILTY, AND MULTIMORBIDITY

### 2.1.1. Concept of frailty syndrome

The word frailty is derived from the Latin *'fragilita; bittleness'* which means 'weakness'. It is literally defined as the quality of being easily broken. Theoretically, frailty is defined as being a multi-systemic reduction of reserves at the functional level resulting in the limitation of the body's ability to respond to stress, even minor (9,48).

The concept of frailty evolved through its initial publication in a literary geriatric journal at the end of the 20th century (49). Between 1970 and 1980, frailty referred to stunting and concepts of institutionalization (49,50)**.** As early as the end of 1980, a description was made of frailty as being closely linked to the concepts of comorbidity and handicap (50). Later, comorbidity and disability were independently differentiated from frailty. Subsequently, the identification and definition of a set of criteria was established to distinguish the different conditions from each other; from where a call was launched for the determination of the criteria of identification of the frail people (7,51). At the dawn of the 21st century, the conceptualization of frailty has been variously established through numerous assessment tools (8)**.**

Over the last decade, the definition of frailty has remained unconventional so that in the literature, two major models of frailty have been described together with assessment tools:

- The first model represents the frailty phenotype or phenotypic frailty established from the Cardiovascular Health Study (CHS) by Fried et al (9).
- The second model represents the frailty index. This model alludes to the identification of cumulative deficits during a geriatric assessment. The accumulation of deficits alludes to an array of polymorphic symptoms and diseases that occur during aging (51).

This frailty review focused on the first model, specifically the frailty phenotype described by Fried et al (9). Its phenotypic criteria were applied to the assessment of frailty in the current study.

### 2.1.2. Concept of Multimorbidity

Etymologically, the term multimorbidity is derived from the expression *''multi- + morbidity''* alluding to the Latin expression *''morbidus''* which means *''diseased''* or *''morbus''* meaning *''disease''*. Morbidity literally means the quality of being sick or unhealthy. Multimorbidity is defined as the presence of more than two long-term health condition or chronic disease (5).

Many initiatives have been the subject of notorious debates on the heterogeneity of health states in the conceptual definition of multimorbidity since the end of the 20th century. Originally, the concept of multimorbidity was inadvertently attributed to comorbidity which was coined by Feinstein in 1970 for the first time. As early as 1976, the use of the term multimorbidity was initiated by Brandmeier and Franke in Germany for the first time. In 1996, the clarification of the definition of the two terms comorbidity and multimorbidity was proposed by Van den Akker et al., with the aim of removing the growing ambiguity on the use of the two terms.

Since 2013, multimorbidity has been attributed to the combination of at least two acute or chronic disease, or somatic or biopsychosocial risk factor by Jean Yves et al. In 2016; multimorbidity has been defined by the WHO as the coexistence of two or more chronic diseases in the same person (5). However, the concept of MLTC had not been clarified (6). Following the official WHO definition, a workshop was organized in South Africa in 2016 by the South African Academy of Science and the United Kingdom Academy of Medical Sciences with the aim of conceptualizing the MLTC (6). Academics joined the WHO definition with specific clarification of chronic conditions. NCDs, mental health, and infectious diseases (Human immunodeficiency virus (HIV) and tuberculosis) of long duration have been identified as chronic conditions (6). In addition, the definition of multimorbidity has been expanded on the origin of the coexistence of chronic conditions to identify concordance and discordance of conditions (6). Concordant multimorbidity refers to the coexistence of conditions with similar origins or treatments. As for discordant multimorbidity, it concerns conditions that have no relationship independently with each other(6). The use of the MLTC concept has been best indicated with the aim of facilitating a better understanding of multimorbidity by the public and patients. This multimorbidity review has focused on MLTCs.

## 2.2. METHOD FOR ASSESSING FRAILTY AND MULTIMORBIDITY

### 2.2.1. Physical frailty phenotype assessment criteria

The model of phenotypic physical frailty was assessed based on the low level of cellular and molecular dysregulation involved in each physiological system. The model is composed of five criteria determined as follows in **Table 2.1** (9)**.**

**Table 2.1:** Physical frailty phenotype assessment criteria

| Characteristic of frailty | Evaluation criteria |
|---|---|
| **Muscular weakness** | Grip strength: lowest 20% by gender and body mass index. |
| **Slow walking speed** | Walking time/15 feet or 4.57 m: slowest 20% by gender and height |
| **Low physical activity** | Energy expenditure: 20% lowest by gender, <383 kcal/week (men) and <270 kcal/week (women). |
| **Exhaustion/low endurance** | Self-reported exhaustion from the Centre for Epidemiological Studies Depression Scale, 3-4 days/week or most of the time. |
| **Involuntary weight loss** | Involuntary weight loss or malnutrition > 4.5 kg in the previous year. |
| **Frailty score: 0 to 5** | Non-frail (0 criteria present); Pre-frailty (1-2 criteria present); Frailty (≥ 3 criteria present) |

### 2.2.2. Multimorbidity assessment

Many tools have been designed to comprehensively compile the list of commonly reported MLTCs. These include the Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC). The common assessment of multimorbidity in epidemiological studies is based on MLTCs diagnosed in participants such as (6):

- NCDs defined and reported;
- Mental Health Diseases;
- Chronic infectious diseases

In addition, substance abuse and alcohol consumption have been considered as MLTC as well as certain complex symptoms of chronic pain, sensory, visual and auditory disorders.

The coexistence of one to two or more reported MLTCs was considered an endpoint for multimorbidity in this review.

## 2.3. EPIDEMIOLOGICAL ASPECTS OF FRAILTY, AND MULTIMORBIDITY

### 2.3.1. Global distribution of frailty, and multimorbidity patterns

Overall estimates of frailty, and multimorbidity are reported variably across assessment settings. Most studies have been conducted in adults aged 65 and over living in communities, although there are a few rare studies conducted in hospitals. Many studies have been conducted in LMICs and in high-income countries (HICs). On the one hand, the pooled prevalence of frailty in HICs and LMICs was 3.5-8.1% and 14.4-20.7% respectively (13,19). On the other hand, the pooled prevalence of multimorbidity in HICs and LMICs was 32.5–44.3 and 26.4–36.8, respectively (15,16). Studies have reported an overall frailty of 10-37% in African countries; 15-19% on the American continent; 10-12% in Asian countries; 7-10% in European countries; and 8-16% in Oceania**.** Similarly, multimorbidity has been estimated at 28-52.8% in European countries (52) and 30-55% on the American continent (53,54); 32-40% in Asia countries (53).

The pilot study evaluating frailty estimated the prevalence of frailty at 7% (9). As for multimorbidity, analyses have reported that the prevalence is constantly increasing, varying between 55-98% (55,56). It remains commonly observed in adults over 65 years old. Among 120,805 non-frail adults, the overall estimate of the combined incidence of frailty in a meta-analysis was 43.4 cases per 1000 years- people, where 13.6% had become frail in 3 median follow up years (31). Similarly, the incidence of pre-frailty in healthy people defined as robust people was 150.6 cases per 1,000 person-years, of which 30.9% had become pre-frail in 2.5 median follow up years (31). Furthermore, the overall combined incidence of multimorbidity in a systematic review was estimated at 30.7 cases per 1000 person-years, of which the cumulative median incidence was 2.8% (32). Additionally, analyses showed that 70% of frail adults developed multimorbidity, while 16% of multimorbid adults were frail (42). **Figures 1** and **2** present the global prevalence.

### 2.3.2. Distribution of frailty, and multimorbidity patterns in sub-Saharan Africa

Seventeen SSA countries have data reported in the literature, so that the care of the elderly remains a problem that has been the subject of qualitative studies in Namibia and South Africa (13, 16-21, 43)**.** Apart from South Africa and Burkina Faso, studies on frailty and multimorbidity have been reported in seven to eight SSA countries from 1998 to 2022. On the one hand, the prevalence of frailty was estimated at 9.7-50% in Lesotho among people aged over 65 (57); and 64.7% in HIV-infected populations in Zimbabwe in 2022 among people aged over 30 (58). It ranged between 4.4–

14.12% among people aged over 60 in Tanzania up to 2018 (43). On the other hand; multimorbidity was estimated at 3.4-5.4% among participants over 15 years of age in Botswana in 2020 (35,59). It has been described in varying proportions between 19.6 and 54.8% among people aged 40+ in Ethiopia from 2018 to 2021 (60) and between 25.3 and 73.8% among people aged 40+, and 60+ in Tanzania (61,62). In addition, the estimate of multimorbidity in four African countries among people aged 40 to 60 was 47.2% and 35% respectively in women and men (18). Multimorbidity among men and women in this study was 51.7% and 64.9% respectively in South Africa; 31.3% and 48.4% in East Africa (Kenya); and 20.2% and 24.1% in West Africa (Ghana and Burkina) (18). Most studies in SSA have been reported on NCDs such as cardiovascular, chronic respiratory, chronic renal, and mental diseases; diabetes and neoplastic conditions (11,63). According to WHO, 80% of premature deaths were caused by NCDs (11). Indeed, in Senegal, chronic diseases accounted for 32-40.3% among people aged 20+ compared to 26.8% of NCDs among people aged 40+ reported in Burkina Faso (64,65). In addition, the analysis done by Micklesfield et al.; in the four countries estimated that dyslipidaemia and hypertension were frequently observed in South African women aged 40 to 60 (25% against 21.6%) (18). **Figures 2.1** and **2.2** present the global prevalence.

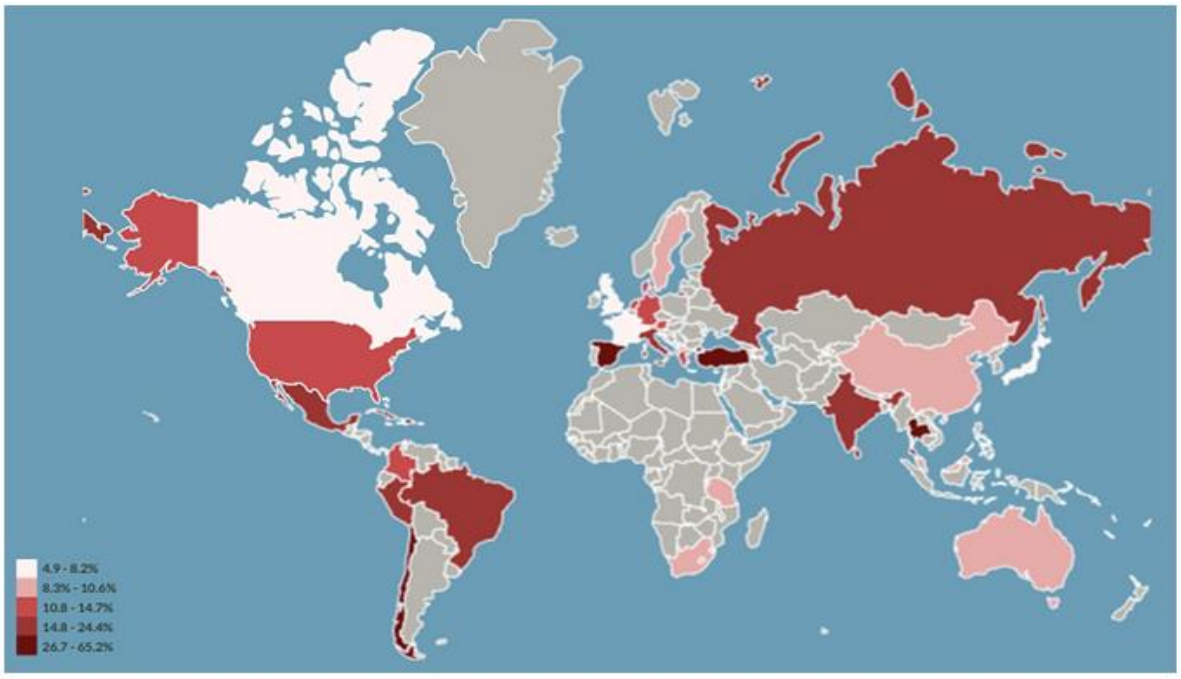



**Figure 2.1**: Global distribution of the prevalence of phenotypic frailty in adults over 60 years old. Source : Zeinab Majid et al. 2020 (13).

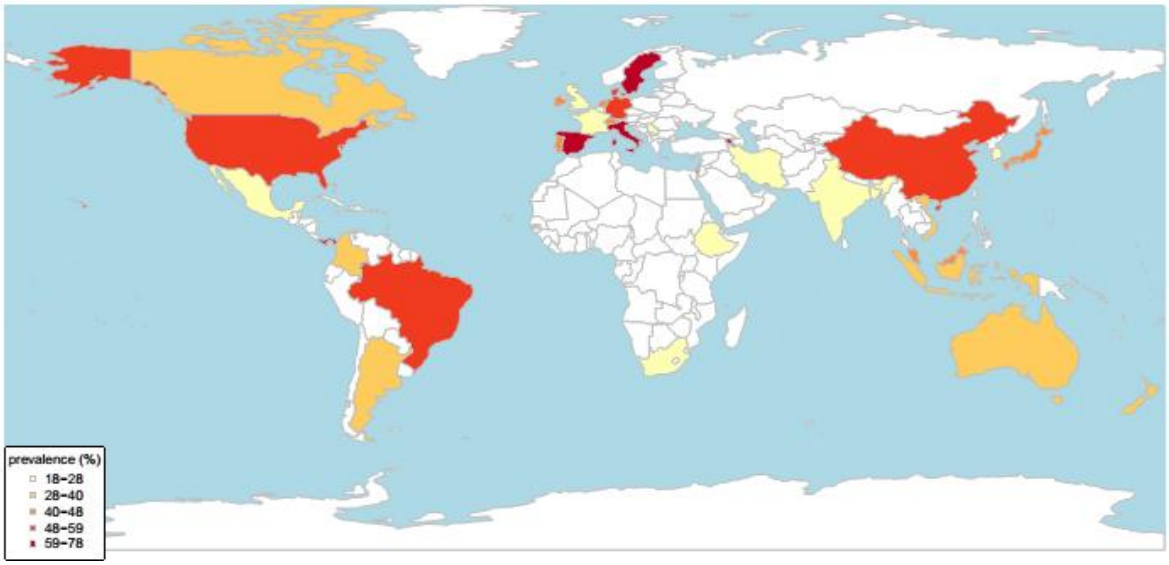



**Figure 2.2:** Global distribution of the prevalence of multimorbidity.

Source: Iris SSH et al., 2021 (16).

### 2.3.3. Distribution of frailty, and multimorbidity patterns in South Africa

In rural South Africa, frailty was estimated at 5.4–13.2% in 2017 and risk factors were increasing age and female gender (21)**.** In KwaZulu-Natal, pre-frailty and frailty were 81% and 7-9.28%, respectively (66). At the same time in 2021 in the district of Agincourt, multimorbidity of 70.9% was associated with socio-demographic factors such as increasing age and the high risk of mortality (67)**.** Additionally, a systematic review of studies conducted up to 2020 estimated multimorbidity at 3–23% and 30–87% in young and old people, respectively (68)**.** In this review; diabetes, hypertension, tuberculosis and HIV were frequently identified (68)**.** Further analysis reported that increasing age and female gender (OR 2.73) were the 20.7% risk factors for multimorbidity in participants older than 15 years. On the other hand, the higher level of education (OR 0.72) and an employment OR (0.8) played a protective role (23). Furthermore, a recent analysis carried out in four African countries reported a 66.6% higher prevalence of multimorbidity in South Africa compared to other countries (18). This prevalence was higher in women (64.9%) compared to men (51.7%) (18). The risk of this multimorbidity was associated with age and body mass index in women and men, while physical activity and smoking were differentiated according to the gender of the participant (18).

### 2.3.4. Distribution of frailty, and multimorbidity patterns in Burkina Faso

In Burkina Faso, multimorbidity was reported at 65% in 2016 in urban areas (28). In this study increasing age (Age ≥70 with OR 1.65) was a predictive factor while hypertension, visual impairment, malnutrition, osteoarthritis and diabetes were common chronic conditions (28). In 2019 in the rural area of Nouna with 2,973 participants over the age of 40 from the Heidelberg Aging Study (CHAS); pre-frailty and frailty were reported at 44% and 7% respectively (26). Frailty was mostly reported in women (8%) and predictors were daily activities, family income, single marital status, diabetes mellitus, tuberculosis, heart disease and hypertension (26). In the CHAS study, a multimorbidity of 22.8% was reported. It was estimated mainly in elderly women, single people and people with a high level of education. Frailty has been identified as a predictor (27). The health care experience of these participants was assessed with NCDs proportions of 26.8%; 56.3% pre-frailty and 23.9% medical consultation (65). Moreover, the recent epidemiological analysis carried out in four African countries (South Africa, Kenya, Ghana, Burkina Faso) reported a 21.2% lower prevalence of multimorbidity in Burkina Faso compared to other countries (18). This prevalence was higher in women compared to men (18).

## 2.4. PATHOPHYSIOLOGY OF RISK FACTORS FOR FRAILTY, AND MULTIMORBIDITY

### 2.4.1. Biological and physiological mechanisms of frailty

The physio-pathological mechanism of frailty is characterized by multi-systemic dysregulations. This results in a loss of the homeostasis mechanism accompanied by a reduction in the reserve; resulting in an increase in vulnerability to mortality and morbidity (9,69,70). Many multifactorial causes have been implicated in the dysregulation of physiological systems including: chronic inflammation; activation of the immune, musculoskeletal (sarcopenia) and endocrine systems (9,69). In addition, genetic/epigenetic factors; metabolic and environmental factors; lifestyle factors and chronic diseases potentially contribute to the physiological dysregulation of systems. The immediate consequence is the impairment of the complex adaptation of normal behaviour (9,69,70). The interaction of the different factors coupled with molecular and cellular aging processes contributes to the development of frailty (9,69,70). The end result is frailty which manifests as the syndrome of a constellation of slowness, weakness, low energy, reduced activity

and involuntary weight loss (9,69,70). The combination of at least three criteria contributes to the increased risk of death. **Figure 2.3** summarizes the pathophysiological mechanism cycle of frailty.

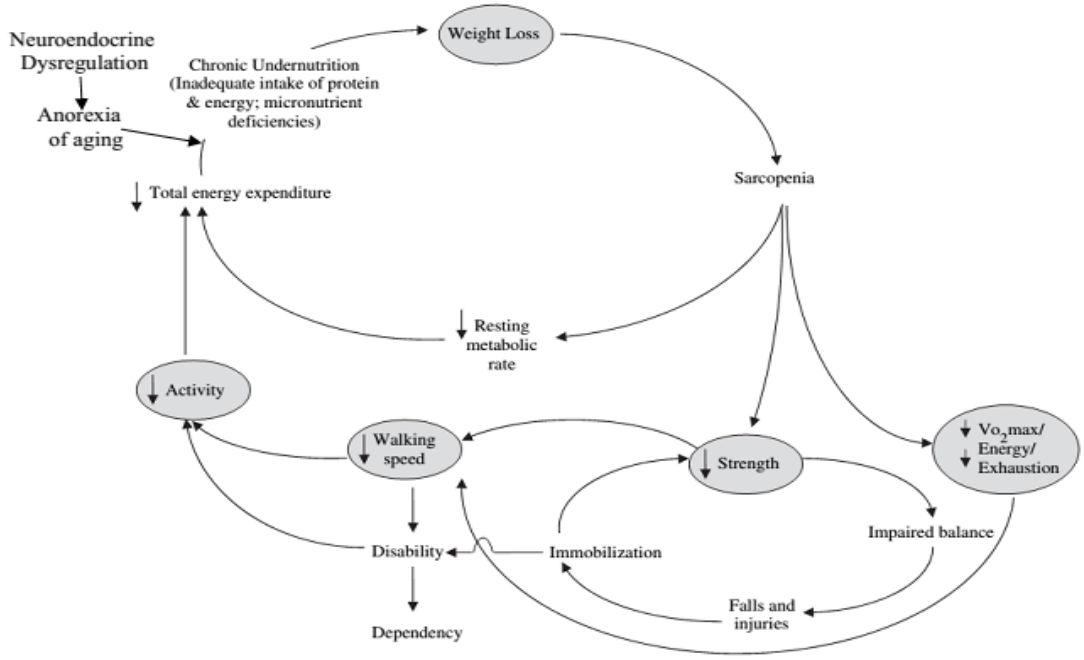



**Figure 2.3**: Cycle of frailty; adapted with permission

Source: Fried, L.P. and Walston, J. (1998) (69). V O2max: maximum oxygen consumption

### 2.4.2. Biological and physiological mechanisms of Multimorbidity

The biological mechanism of multimorbidity has been identified through signalling pathways and cellular cytopathology involving inflammation and oxidative stress (71–73). Indeed, partial mediation via cellular signalling pathways between different physiological systems has been described as a direct consequence of clustering and interaction of MLTCs (72). This results in an acceleration of the normal aging process (72). The mechanisms commonly identified at the level of these MLTCs have been highlighted through: cellular senescence followed by telomeric shortening; PI3K-AKT-mTOR activation-type signalling; autophagic impairment; mitochondrial dysfunction; stem cell depletion, modifying epigenetics; non-normalization of microRNA profiles; low-grade immune-senescence and chronic inflammation (72–74). In addition, the interaction of additional personal factors such as oxidative stress, inflammation and malabsorption of mineral salts have contributed to the occurrence of pathological conditions defining multimorbidity (71–73).

### 2.4.3. Aging, frailty, and multimorbidity

The involvement of aging in the mechanism of homeostatic dysregulation plays a major role in the occurrence of frailty and multimorbidity (75). The association between aging, frailty, and multimorbidity is due to pro-inflammation induced by increased interleukin (IL-6); a targeted biomarker to detect chronic conditions in the elderly (76)**.** Interleukin (IL-6) has been assessed as one of the predictors of disability; mortality and adverse effects observed in the elderly **(76)**. In addition, the chronic oxidation of stress and the depletion of anti-aging molecules (72) have been mainly reported as being at the base of the aging process (72). The analyses reported the major role of the characteristics and pillars of aging in the occurrence and progression of frailty (75). Seven pillars have been attributed to aging in the occurrence of frailty including: adaptation to stress, epigenetics, inflammation, damage, metabolism, proteostasis, stem cells and regeneration (72,75,76). From these pillars of aging there follow three main characteristics of aging such as: The primary characteristics trigger the aging process in the form of damage by proceeding through: genomic instability, epigenetic alterations, telomere attrition and loss of proteostasis (72,75,76). Antagonistic features mediate the mechanism through protective compensation involving deregulation of nutrient sensing, mitochondrial dysfunction, and senescence (72,75,76). The integrative characteristics lead to tissue dysfunction and the occurrence of chronic diseases by proceeding through the depletion of cell strains and the alteration of intercellular communication (72,75,76).

## 2.5. RISK FACTORS ASSOCIATED WITH FRAILTY, AND MULTIMORBIDITY

The main groups of factors associated with the onset and progression of frailty, and multimorbidity that have been identified are socio-demographic determinants, lifestyle determinants, clinical determinants, and biological determinants. From the analysis of the conceptual framework on the mechanism of onset and progression of frailty or multimorbidity, it appears that frailty evolves in different levels from a robust individual to a frail individual. As for multimorbidity, the association of the number of chronic diseases describes its progression. Firstly, the socio-demographic determinants act on the lifestyle determinants thus favouring the consumption of substance, alcohol and sedentary lifestyle. Similarly, there is an interaction between lifestyle determinants and biological determinants that cause clinical manifestations at the organic level after exposure to

external and internal stressors. Following the clinical manifestations come the stage of chronic disease episodes. Moreover, the interaction between chronic diseases and socio-demographic determinants predisposes to a set of events such as early aging, unemployment and death of a spouse. All of these determinants will favour the occurrence of frailty or multimorbidity. Ultimately, the bidirectional relationship between frailty and multimorbidity is likely explained by the fact that an individual with multimorbidity becomes frail and vice versa. **Figure 2.4** presents the conceptual framework of the interrelationships between variables.

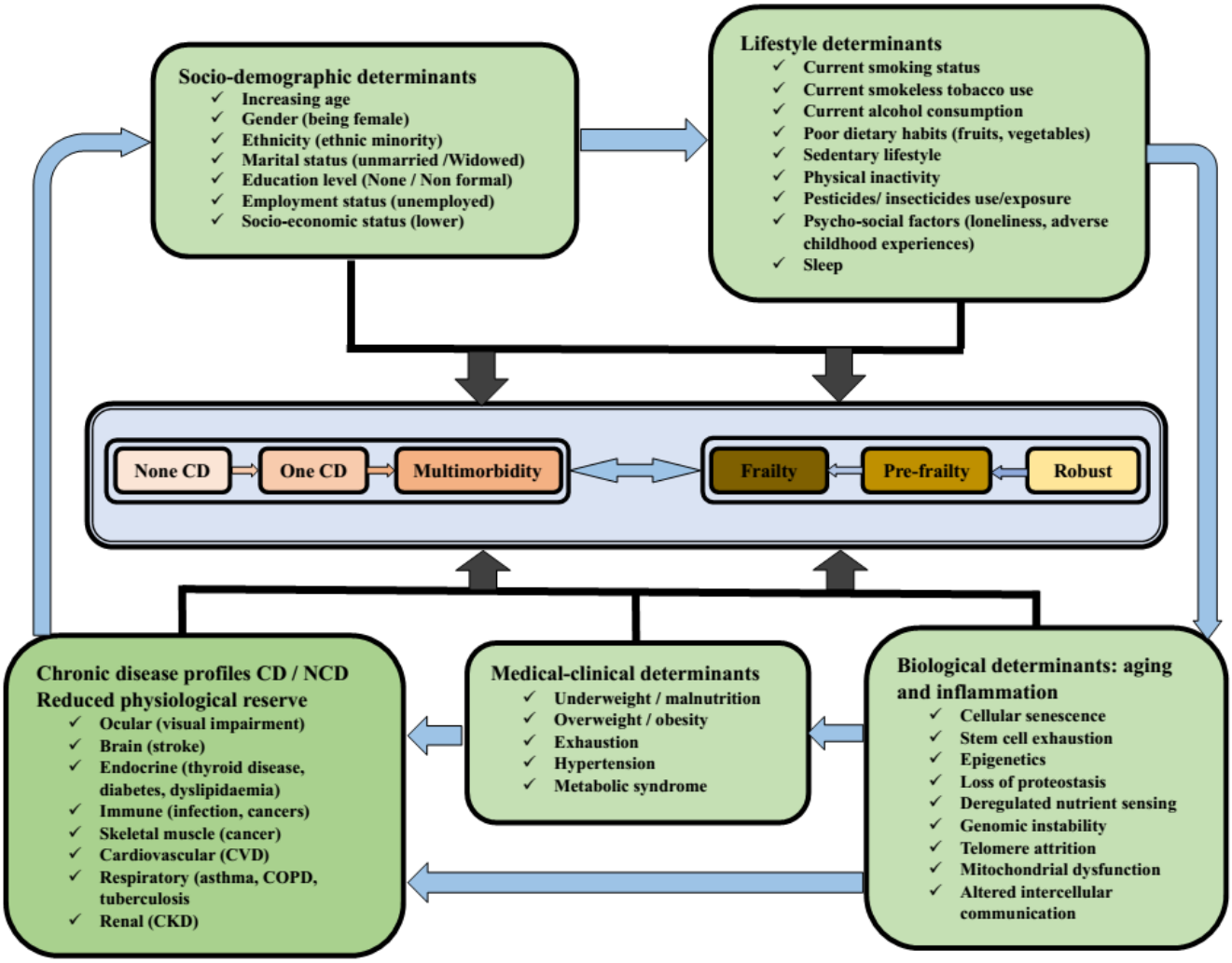



**Figure 2.4:** Conceptual framework of interrelationships between variables.

CD: chronic disease. NCD: non-communicable disease. CVD: cardiovascular disease.

COPD: chronic obstructive pulmonary disease. CKD: chronic kidney disease.

### 2.5.1. Risk factors associated with frailty

#### 2.5.1.1. Sociodemographic determinants of frailty

The prevalence of frailty increased significantly with advanced age over 65 (9). In epidemiological studies, frailty is observed more frequently in women than in men (9,13,20). Similarly, ethnic minorities have been identified as having a high susceptibility to developing frailty (9,13). In addition, being single, divorced or separated has been identified as a determinant in the onset of frailty (26,77). The low level of education of the participant has been identified as a factor in the occurrence of frailty (9,13). The fact of being unemployed or having a socioeconomic status with low income intervenes in the occurrence of frailty (9,13,26,34,77).

#### 2.5.1.2. Lifestyle determinants of frailty

The risk of onset of frailty has been correlated with an unhealthy behavioural context such as smoking, smokeless tobacco use, alcohol consumption, malnutrition, physical inactivity and exposure to pesticides (34,36,77). In many studies, smoking and alcohol consumption have been predictors of frailty (34,77). Moreover, the risk of frailty was weakly associated with a diet made up of fruits and vegetables (38,57,78). The increased risk of frailty has been correlated with vitamin D deficiency and deficits in total protein-calorie intake (78,79). The risk of developing frailty has been associated with physical inactivity (36). Similarly, physical exercise has been shown to help delay the development of frailty in people aged 65 and over (36).

#### 2.5.1.3. Clinical determinants of multimorbidity

Underweight, reflecting malnutrition, has been identified as a factor associated with frailty (57,77,80). Diabetes mellitus and obesity conditions have been significantly associated with the occurrence of frailty (34,77). The growing increase in chronic diseases has been incriminated as a major determinant of frailty (9,26,34). Frailty was frequently increased in individuals with clinical conditions of chronic infectious disease, chronic inflammatory disease, chronic respiratory disease (34,77). Similarly, frailty was correlated with increased cardiovascular disease and arterial hypertension (34,58). Rheumatic arthritis has been identified as a factor associated with frailty (81). In numerous analyses, multimorbidity has been identified as a contributing factor to frailty in the elderly (34,42).

### 2.5.2. Risk factors associated with multimorbidity

#### 2.5.2.1. Sociodemographic determinants of multimorbidity

Advanced age over 65 has been associated with a risk of developing multimorbidity, so chronic disease and aging occur proportionally (18,33,55). Similarly, being a woman has been identified as a risk for the occurrence of multimorbidity (18,27,33). On the other hand, the conclusions of numerous studies on marital status as a risk factor have been variously reported (59,82,83). Participants in a situation of divorce, widowhood or separation had a higher risk of developing multimorbidity than other participants (84). Also, the level of education has been variously evaluated in the occurrence of multimorbidity (23,27,83). The low level of education exposed to the occurrence of multimorbidity while the high level of education remained a protective factor of multimorbidity (23,83,85). In addition, low socioeconomic status related to financial hardship among participants was established as a risk for the development of multimorbidity (23,33,84).

#### 2.5.2.2. Lifestyle determinants of multimorbidity

The current consumption of tobacco and alcohol has been identified as a predisposing factor for multimorbidity (23,82,85). In a study conducted in Botswana, alcohol consumption was identified as a predisposing factor for multimorbidity (59,82). Similarly, the fact of not smoking has been identified as a factor that may limit the occurrence of multimorbidity (82,85). Multimorbidity has been frequently observed in people with a low-calorie diet and insufficient in fruit and vegetables (82). On the other hand, the reduction in the risk of multimorbidity was associated with the consumption of vegetables, fruits and whole grain products (33,82,86). Physical inactivity has been identified as a major determinant in the occurrence of multimorbidity (33,36). Increased risk of multimorbidity has been associated with environmental exposure (33).

#### 2.5.2.3. Clinical determinants of multimorbidity

Increased BMI was significantly associated with increased risk of multimorbidity (18,82). Overweight or obesity have been reported as contributing factors to multimorbidity (33,59,82). Indeed, the existence of a history of mental disorders, hypertension, cancer, arthritis, osteoporosis and asthma has been assessed as a risk of the development of multimorbidity (60,87). The analyses reported that, the interaction of type 2 diabetes with tuberculosis infection increased the risk of developing multimorbidity. Similarly, the existence of tuberculosis has been evaluated as a

predisposing factor for gluconic intolerance at the origin of the development of type 2 diabetes. Ultimately, the risk of developing multimorbidity was strongly associated with frailty (27,42).

# CHAPTER 3: METHODS

This chapter describes the different methodological approaches used in the description and determination of risk factors associated with frailty and multimorbidity patterns at the socio-demographic, lifestyle and medical-clinical levels. The methodological description refers to middle-aged adults between 40 and 65 years old in a rural population of Burkina Faso. The chapter mainly describes the methodological parameters such as the context and setting where the study was carried out, the study population, and the sampling. Likewise, the collection and statistical analysis of the data are described as well as the ethical considerations.

## 3.1. Description of primary study

The data included in this study were part of the Africa Wits-INDEPTH Partnership for Genomic Research (AWI-Gen) project, through the consortium, Human Heredity and Health in Africa (H3Africa). The project aimed to examine the genomic and environmental factors that interact with the physiology and behaviors of individuals to influence the risk of cardio-metabolic diseases. AWI-Gen study was a cohort study that was conducted in the following centers such as: Agincourt, Dikgale, Soweto (South Africa); Nanoro (Burkina Faso); Nairobi (Kenya); Navrongo (Ghana).

In Burkina Faso, the sub-study was conducted by the Clinical Research Unit of Nanoro (CRUN) through its Health and Demographic Surveillance System (HDSS) in two health districts between 2015-2022. At the baseline study, participants were recruited between 2015 and 2016. The participants were reviewed at the follow-up visit between 2020 and 2022. The study population consisted of participants, regardless of gender, who were between the ages of 40 and 60 at the time of the baseline visit between 2015-2016 and who agreed to participate in the follow-up visit between 2020-2022. Similarly, participants who were pregnant at the time of the study were excluded. Data collection procedures have been provided in detail in the reference documents (88). The baseline study involved a group of 2094 participants. After follow-up, 1500 participants were included in the follow-up visit between 2020-2022. We considered in this analysis only participants who completed the initial and follow-up visit.

## 3.2. Study design

We performed secondary data analysis using data from the AWI-Gen sub-study, a retrospective cohort study with the aim of identifying socio-demographic factors, lifestyle factors and medical-clinical factors involved in the occurrence of frailty and multimorbidity patterns. The data was used to assess the cumulative incidence associated with changes in socio-demographic conditions, lifestyle conditions and medical-clinical conditions after an initial assessment of multimorbidity without analysis of frailty at the baseline study. Middle-aged adults 40 to 65 over the period 2015-2022 in the rural population of Burkina Faso were the target of this secondary analysis.

## 3.3. Study setting

The data included in this study come from the AWI-Gen sub-study conducted by the Clinical Research Unit of Nanoro through its HDSS in the Health District of Nanoro and Yako in Burkina Faso. CRUN is part of the Health Science Research Institute of the Centre-West Regional Direction (IRSS/DRCO). CRUN is one of the 4 institutes of the National Center for Scientific and Technological Research (CNRST) attached to the Ministry of Higher Education. Since its creation in 2008, the institute has conducted more than 20 phase 2, 3, 4 clinical trials, two vaccine trials, 2 community-based trials as well as several fundamental research projects.

The Health District of Nanoro is one of the 70 districts in the country. It is located 90 km from the city of Ouagadougou and has 180,357 inhabitants, 24 villages. The HDSS covers 07 Health and Social Promotion Centers (CSPS) attached to the Medical Center with Surgical Unit (CMA) of Nanoro. The Health District of Yako has 113,992 inhabitants, 254 administrative villages. It is located 110 km from the capital Ouagadougou. The Health District of Yako has 54 health facilities and a Medical Center with a Surgical Unit. **Figure 3.1** presents the health facilities of the health district of Nanoro and Yako in Burkina Faso.

## 3.4. Study population

The study population consisted of adult participants aged between 40 and 65, regardless of gender, residing in the two health districts (Nanoro and Yako) in Burkina Faso during the period from 2015 to 2022. The selection of participants for this secondary analysis was based on the inclusion and exclusion criteria of the baseline and follow-up visit. Thus, all participants who were recruited at the baseline and follow-up visit of the sub-study were included in this secondary data analysis for the present study. Cohort participants who did not consent or who were unable/unwilling to answer

questions at baseline or follow-up visit were excluded from secondary analysis. Similarly, participants who were pregnant at the time of the study visits were excluded from the analysis.

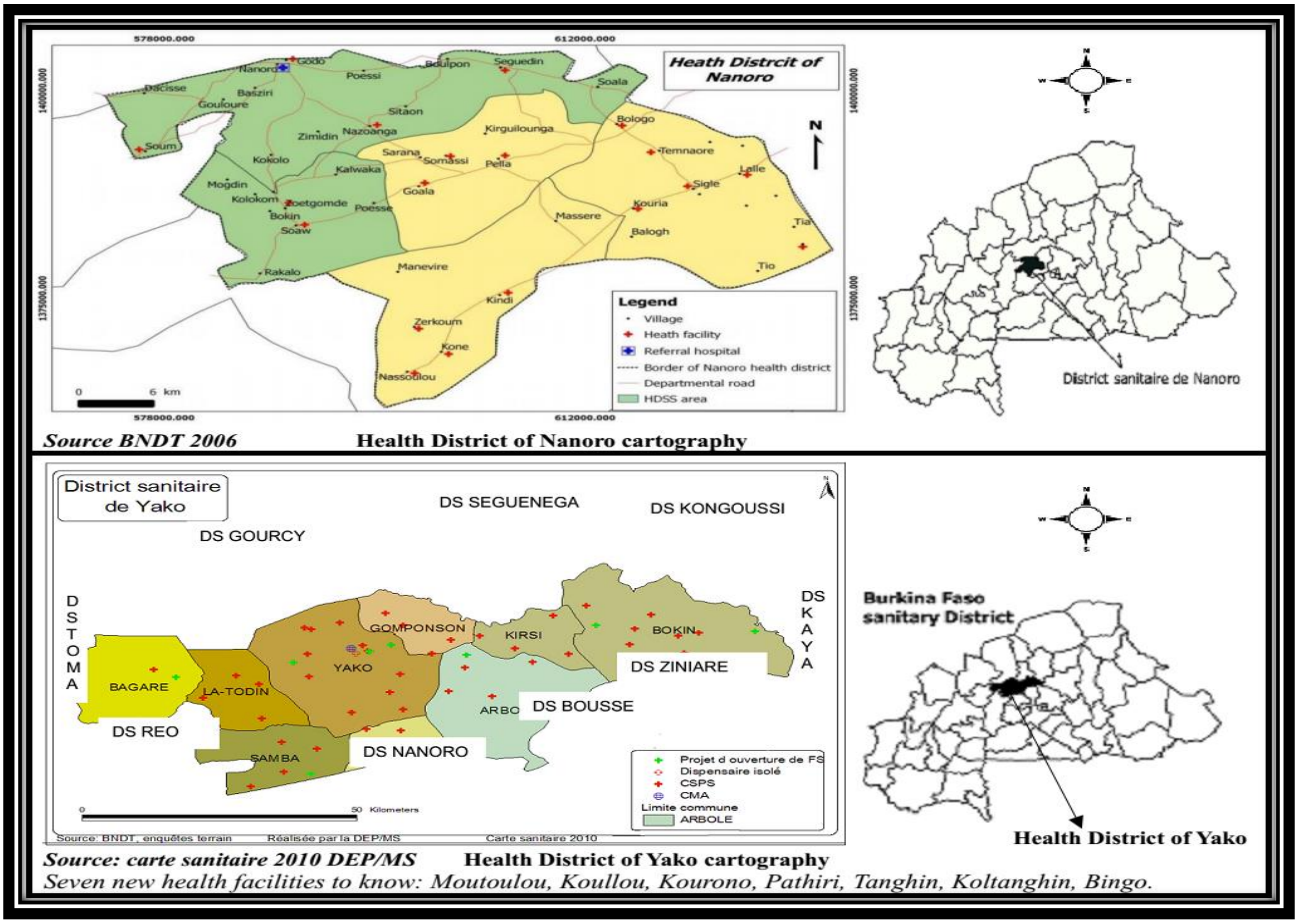



**Figure 3.1:** Health District of Nanoro and Health District of Yako cartography

## 3.5. Study sample

The prevalence of frailty and multimorbidity estimated in a rural study in Nouna, Burkina was 8.0 and 22.8%, respectively, with an odds ratio of 1.98 (1.57-2.50) (27). The baseline study which took place between 2015 and 2016 recruited 2,100 participants. After five years of follow-up, 1500 participants were included in the follow-up visit between 2020 and 2022. Assuming that multimorbidity increases the risk of developing frailty or vice versa and assuming that the study could detect an effect in log(1.98) = 0.68 for a size of 1500 participants with a two-sided significance of 5%; the probability (power) that there was a real clinical or biological difference or association between frailty and multimorbidity was 98.62%. Therefore, a sample size of 1500 after cleaning the database was adequately representative to test the hypothesis.

## 3.6. Study data collection

### 3.6.1. AWI-Gen sub-study data collection

Data collection of the main sub-study was done through face-to-face interviews in accordance with the recruitment procedures established on the CRUN setting. Recruitment was done by trained agents. Informed consent was obtained by signature and/or fingerprint of the participant, assisted by a witness. Each participant was asked to complete a standardized and structured questionnaire on socio-demographic information, lifestyle information, anthropometric, medical-clinical, and biological information. The questionnaire was administered for approximately 45 minutes in the language of the participants (Mooré, Dioula, Gourounsi, French).

Each participant was asked to complete socio-demographic information such as age, gender, ethnicity, level of education, marital status, and employment status. The lifestyle of each participant was assessed through smoking status, smokeless tobacco use, alcohol consumption and alcohol problematic (89). The assessment of problematic of alcohol use was based on the CAGE questionnaire (89). Similarly, food and dietary habits on the consumption of fruits, vegetables and foods rich in carbohydrates were evaluated. The three domains of physical activity (transport-related, occupational, and leisure) were evaluated using the standard Global Physical Activity Questionnaire (GPAQ) (90,91). Each participant was asked to describe the history of their exposure to pesticides and insecticides. Clinical measurements of blood pressure, heart rate, height, weight, hip and waist circumference were performed. An abdominal and carotid ultrasound was performed by a physician. A spirometry test was performed.

On the other hand, each participant was invited to perform physical performance and frailty components measurements. Therefore, each participant was asked to perform grip strength (Jamar Dynamometer), walking speed, and ability to rise from standing/sitting. Furthermore, health habits and self-rated health status by a health worker on twelve conditions were provided. These conditions were cancer, current tuberculosis, asthma, COPD (emphysema, chronic bronchitis, chronic lung disease), visual impairment, diabetes mellitus, hypercholesterolemia, hypertension, thyroid diseases, chronic kidney diseases and rheumatic arthritis. Also, CVD events (stroke/mini-stroke, angina, heart attack, congestive heart failure) were provided. At the biological level, blood and urine samples were obtained by the nurses from all fasting participants for biochemical analysis of serum albumin, lipids, glycemia and serum creatinine. Anonymity was applied for the confidential conservation of the data.

### 3.6.2. Secondary study data collection

As part of student training, investigators of CRUN research studies allow students access to data to support their training. Permission has been granted by the AWI-Gen project investigators and site data gatekeeper (CRUN) of Burkina Faso. The selection of data for secondary analysis was made based on the specific data collection procedures in the different stages of recruitment described above, ranging from obtaining informed consent to reporting results from participants to the main study. Anonymity was applied for the processing and confidential storage of the data.

## 3.7. Data management

### 3.7.1. Data processing

Data from the main sub-study was recorded in the purpose-developed REDCap database where basic quality control (QC) testing was performed. Additional QC was performed using the PostgreSQL database after exportation. Additional processing was performed using Stata version 17 software to conduct secondary data analysis. Any data or observation with a value that was very far from or abnormally different from other values measured under normal conditions was declared an outlier. Thus, missing data, 2 outliers were removed and corrected. The missing data of certain exploratory variables were the subject of a sensitivity analysis through multivariate normal distribution (MVN) of multiple imputation. The socio-demographic, lifestyle, medical-clinical and biological variables collected were recoded into several modalities. **Table 2** presents the description of the categorical or numerical character of the exploratory variables. The variables determining frailty and multimorbidity as the first and second main outcome respectively were recoded into multilevel dichotomous variables.

**Table 3.1: List of exploratory variables**

| Variables | Definitions | Categories/ Dichotomization of variables |
|---|---|---|
| **Sociodemographic characteristics** | | |
| **Age** | Number of years | Age, age group (40 to 49); (50 to 59); (60 to 65) |
| **Gender** | Birth sex | Female; Male |
| **Ethnicity** | Original ethnicity | Mossi; Gourounsi; others |
| **Marital status** | Being married / living together | Unmarried; Married/cohabitating; Widowed |
| **Education level** | Study completed | None/Non formal; Primary; Secondary; Tertiary |
| **Employment status** | Occupation in last 12months | **Yes** (Self-employed, full-time, part-time employed, informal); **No** (retired, employed) |
| **Lifestyle characteristics** | | |
| **Smoking status** | Smoking cigarettes, cigars/pipes | Never smoked; Former smoker; Current smoker |

| | | |
|---|---|---|
| **Smokeless tobacco use** | Snuff or chewing tobacco use | Never used; Former user; Current user |
| **Alcohol consumption** | Alcohol drink (beer, wine, spirits, traditional (Dolo). | Never drink; Former drinker; Current drinker |
| **Problematic of alcohol** | | Current non problematic; Current problematic |
| **Food & diets habits** | Fruits servings per day | Number of servings |
| | Vegetables servings per day | Numbers of servings |
| | Foods rich in carbohydrates | Number of servings |
| **Physical activities** | MVPA (Work, Transport, Leisure). | MVPA in minutes; Low activity; Moderately active; Highly active |
| **Pesticides use/exposure** | Work with or be exposed | Yes; No |
| **Medical-clinical characteristics** | | |
| **Body mass index** | Weight in kg / height in m² | Underweight; Normal-weight; Overweight; Obesity |
| **Metabolic syndrome** | if ≥3 criteria present | Yes (Waist, BP, TG, HDL-C, glucose); No |
| **Chronic diseases** | current chronic disease | Twelve chronic diseases reported |
| **Chronic diseases status** | Number of chronic diseases | None; One chronic disease, multimorbidity (≥2) |
| **Frailty components** | Five components | Weight loss, exhaustion, low PA, walking, grip |
| **Frailty status** | Number of frailty components | Robust (0); Pre-frail (1-2); Frail (≥3) |

MVPA: moderate-to-vigorous intensity physical activity. PA: physical activity. BP: blood pressure. TG: triglycerides. HDL-C: high-density lipoprotein cholesterol

### 3.7.2. Operationalization of frailty definition as dependent variable

We used the original lower quintile approach method applied to continuous variables to operationalize the definition of frailty on the following criteria: weight loss, exhaustion, low grip strength, low physical activity and slow walking speed (9):

**Weight loss** was obtained through body mass index which was evaluated by dividing the weight in kilogram by the square of the height in meters. The classification was made such as: underweight (BMI < 18.5 kg/m2), normal weight (BMI ≥ 18.5 and < 25 kg/m2), overweight (BMI ≥25 and < 30 kg/m2) and obese (BMI ≥ 30 kg/m2). Weight loss was defined as BMI <18.5kg/m².

**Self-reported exhaustion** was measured through an adapted question derived from the Center for Epidemiologic Studies – Depression (CES-D) based on a 5-point scale: "*Do you ever wake up and feel tired*?" The criterion of frailty was present if the participant's response was "3-moderately"' or "4-severely" or "5-very seriously".

**Low physical activity:** the total minutes spent in each of the three domains (occupational, transport-related and leisure) of MVPA per week were calculated (90,91). Low physical activity was defined by the lowest quintile stratified by sex applied as a cutoff point. Similarly, we derived physical activity time in metabolic equivalents-minutes per week (METs) according to GPAQ

criteria (90,91). Therefore, physical activity was categorized as follows: Inactivity/low physical activity (MVPA<600METs); moderately active (600-1200METs); highly active MVPA (>1200METs).

**Slow walking speed**: the measurement of walking speed was made through walking at the usual pace over a course of 5 meters, the walking time recorded in seconds. Slow walking speed was defined by the highest quintile, stratified by gender and height.

**Low grip strength**: the assessment of grip strength was done by asking the participant to squeeze a hand-held dynamometer (Jamar) with the non-dominant hand. An average force measurement in kilograms was derived from the three measurements made. Low grip strength was defined by the lowest quintile stratified by sex and BMI applied as a threshold.

Frailty was identified on the basis of the association of different phenotypic criteria as follows: 0 criteria defining robust individuals, 1-2 criteria defining pre-frail individuals and ≥3 criteria defining frail individuals (9). **Table 3** summarizes the criteria used to define frailty.

**Table 3.2:** Criteria used to define frailty

| **Components** | **Definition** | | | **Criterion** |
|---|---|---|---|---|
| **Weight loss** | The criterion of nutritional frailty was approached by leanness, defined as a **BMI < 18.5 kg/m²** according to WHO thresholds. | | | Yes, frail |
| **Exhaustion** | *"Do you ever wake up and feel tired?"* 1 = None; 2 = Slightly; 3 = Moderately; 4 = Seriously; 5 = Very seriously. Participant answering to either of these question **"3"** or **"4"** or **"5"** | | | Yes, frail |
| **Low physical activity** | Physical activity domain (occupational, transport-related and leisure) using total MVPA minutes or calculated METs. Low activity was defined by the lowest quintile stratified by sex. **Men: MVPA<1470** min/week or **MVPA<5880** METs-min/week **Women: MVPA<2220** min/week or **MVPA<8880** METs-min/week | | | Yes, frail |
| **Low walk speed** | **Stratified by gender and height (gender-specific cutoff a medium height)** | | | |
| | Men height (cm) | Cutoff slow walking | Women height(cm) | Cutoff slow walking |
| | Height ≤ 173 | ≥ 6.70 seconds | Height ≤ 161 | ≥ 8.50 seconds |
| | Height > 173 | ≥ 6.30 seconds | Height > 161 | ≥ 8.10 seconds |
| **Low grip strength** | **Stratified by gender and body mass index (BMI) quartiles** | | | |
| | Men BMI kg/m2 | Cutoff for grip (kg) | Women BMI kg/m2 | Cutoff for grip (kg) |
| | BMI ≤ 19.01 | ≤ 20.67 | BMI ≤ 18.29 | ≤ 15.33 |
| | BMI 19.02 – 21.09 | ≤ 25.00 | BMI 18.29 – 20.12 | ≤ 16.00 |
| | BMI 21.10 – 23.64 | ≤ 24.67 | BMI 20.12 – 22.59 | ≤ 16.00 |
| | BMI > 23.64 | ≤ 26.67 | BMI > 22.59 | ≤ 17.67 |
| **Frailty score: 0–5** | **Presence of criteria: Robust (0 criteria); Pre-frailty (1-2 criteria); Frail (≥ 3 criteria)** | | | |

BMI: body Mass index. WHO: world health organisation. GPAQ: global physical activity questionnaire. MVPA: moderate-to-vigorous intensity physical activity.

### 3.7.3. Operationalization of multimorbidity definition as dependent variable

Multimorbidity was defined by the coexistence of two or more of the following twelve chronic conditions: cancer, current tuberculosis infection, asthma, COPD (emphysema, chronic bronchitis, chronic lung disease), visual impairment, diabetes mellitus, CVD (stroke/mini- stroke, angina, heart attack, congestive heart failure), hypertension, thyroid diseases, chronic kidney diseases, rheumatic arthritis and dyslipidemia. Therefore, the chronic condition status variable was dichotomized into three levels such as: **none chronic disease** (0 chronic disease criteria present), **one chronic disease** (1 chronic disease criteria present) and **multimorbidity** (≥ 2 chronic disease criteria present). Chronic conditions have been defined as follows:

Hypertension condition was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or if the participant was on treatment for hypertension (92). Diabetes mellitus was based on WHO criteria such as the presence of a diagnosis of diabetes previously made by a health professional, or the notion of the existence of a treatment for diabetes, or a fasting blood glucose ≥7mmol/L or random blood glucose ≥11.1 mmol/L (93). Chronic kidney disease was based on the following criteria: estimated glomerular filtration rate (eGFR)<60mL/min per 1.73 m2 (CKD Epidemiology Equation (CKD-EPI), the existence of albuminuria (urinary albumin/urinary creatinine ratio >3 mg/mmol), or the existence of both (94).

Dyslipidemia was based on the following criteria: the presence of a diagnosis of hypercholesteremia (high cholesterol) previously made by a health professional, or the notion of drug treatment modifying lipids, or triglycerides (TG)≥1.7mmol/L, or low-density lipoprotein cholesterol (LDL-C) ≥3.0mmol/L, or high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L for men and <1.3 mmol/L for women, or total cholesterol (TC) ≥ 5.0 mmol/L (95). HDL-C, TC, and TG analysis was performed with Randox Daytona Plus on fasting venous blood samples. The Friedewald equation was used to calculate LDL-C.

The determination of other chronic diseases was based on a self-report of the existence of diseases previously diagnosed by a health professional or the notion of the existence of a drug treatment against the mentioned condition. Thus, the following conditions had been reported: cancer, current tuberculosis infection, asthma, COPD, visual impairment, CVD, thyroid diseases, rheumatic arthritis. Furthermore, obesity was considered a risk factor and was not included as a chronic condition.

### 3.8. Statistical analysis

The description and identification of the factors likely to predict frailty and multimorbidity were investigated using several statistical methods. The description analysis of the study population focused on the socio-demographic, the lifestyle, and the medical-clinical variables in the baseline and follow-up visit. The statistical analysis of the data was carried out using Stata software (version 17). The verification of normality assumption of the continuous variables was carried out a priori, by using the Shapiro-Wilcoxon test, by representing the plots of histograms and the distributional diagnostics plots, and by using the transformational ladder of powers. The medians and inter-quarter range (IQR) were used to summarize the continuous variables whenever possible. Numbers with percentages were used for categorical variables.

A bivariate analysis was performed with a two-sided 5% significance level to assess the association of each level of factors with frailty and multimorbidity, using the different appropriate statistical tests as appropriate. Firstly, the Wilcoxon sign-rank test was used to describe the distribution of continuous variables between the baseline study and the follow-up study. As for the distribution of categorical variables between the baseline study and the follow-up study, we performed the Mac-Nemar test. Secondly, the bivariate association between the dependent variables and the explanatory variables was made using the Kruskal-Wallis test for distributions with continuous variables, the Pearson Chi-Square test and the Fischer's Exact test for categorical variables whenever the conditions were met.

In the multivariate analysis, we applied the regression model to predict the various factors associated with the occurrence of frailty and multimorbidity with a two-sided significance level of 5%. Time-to-event data were not available in the database to explore survival analysis and/or the Poisson regression model. Similarly, the first outcome frailty in the baseline study was not assessed. Since the dependent variable frailty was categorized as an ordered variable, we explored the ordinal logistic regression analysis for appropriate model parsimony. Therefore, odds ratios (OR) with 95% confidence intervals (95%CI) were reported. As for the dependent variable multimorbidity, it had been categorized into three nominal levels. Therefore, we performed a multinomial logistic regression analysis to determine the relative risk ratios (RRR) associated with one condition or multimorbidity considering the reference group the none chronic condition.

Model selection was derived from the stepwise regression approach using variables from the conceptual framework model. For this purpose, the adjustment of OR and RRR with 95%CI were

derived using the backward elimination of variables with nominal p-value ($p<0.2$). The use of directed acyclic graphs (DAG) in appendix 3 made it possible to illustrate the associations and to identify the relevant variables for the adjustment of the OR and the RRR. The variables of the conceptual model with a statistically significant p-value in univariate analysis were selected in the models. However, in the multinomial logistic regression model, the metabolic syndrome variable was not included because of its strong correlation with multimorbidity and its potential confounding effect in the model. Only dependent variables with no missing data were included for analysis. The missing data of certain exploratory variables were the subject of a sensitivity analysis through multivariate normal distribution (MVN) of multiple imputation (Appendix 4). Finally, in the ordinal logistic regression model, we tested the proportional odds assumption of no difference in the coefficients using Brant's test, and that of Rory Wolfe and Bill Gould. Similarly, post-estimation tests of fit statistics exploration were done for the goodness of fit. Pearson's likelihood ratio and chi-square statistic were also used for the goodness of fit.

### 3.9. Ethical considerations

The realization of this study was the subject of a written protocol which was revised after assessment by the group of assessors of the wits school of public health. The protocol was approved by the postgraduate school of the faculty of health sciences of the university of the Witwatersrand. Permission to use AWI-Gen sub-study data for secondary analysis has been granted by investigators at the CRUN (AWI-Gen sub-study clearance certificate numbers: M121029; 015-2014/CE-CM; 2014-08-096; 2020-4-078). The data was treated confidentially, and no effort was made to identify any household or individual respondent interviewed for the study. Unique identification (ID) codes were used to preserve the anonymity of participants so that individual names or household addresses in the data files were not identified. Approval from the University of the Witwatersrand through the *Human Research Ethics Committee (HREC-Medical)* was obtained to conduct this study (study clearance certificate number **M230232 MED23-01-069** in appendix 2).

# CHAPTER 4: RESULTS

This chapter describes the distribution of sociodemographic, lifestyle and medical-clinical characteristics according to the study period on the one hand, and according to the status of frailty and multimorbidity on the other hand. Similarly, the results on the analysis of factors associated with frailty and multimorbidity have been described. The main results were summarized through data tables preceded by a description of the main conclusions.

## 4.1. Distribution of sociodemographic, lifestyle, and medical - clinical characteristics of study participants.

During the baseline study, 2097 participants were included; whose socio-demographic characteristics, lifestyle and medical-clinical characteristics were collected between 2015-2016. Following the five-year follow-up period, 1500 participants participated in the follow-up visit between 2020-2022. Lost to follow-up, deaths and refusals were reported among the 597 participants but these cases were not counted. The socio-demographic, lifestyle and medical-clinical distribution was made among the participants included in the baseline study and reviewed in the follow-up study.

### 4.1.1. Distribution of sociodemographic characteristics, stratified by study period.

Participants in the follow-up study had a median age of 55 years (IQR: 50-60) significantly different from the median age at baseline. The proportion of participants aged 50 to 59 was mostly 51.5% (773/1500) followed respectively by 25.9% and 22.6% of participants who were aged 60 to 65 and 40 to 49. The proportion of women 52.4% (786/1500) was higher than that of men (47.6%). Marital status was mainly made up of 79.4% (1184/1500) of participants who were married or cohabiting. Participants whose partners were deceased were 19.3% (288/1500) while 1.3% were unmarried or divorced or separated. The proportion of non-formal education was 83.9% (1253/1500) and the rest of the participants at all levels had a primary, secondary and tertiary education level. Almost all of the participants 96.8% (1446/1500) held a job of self-employment, full-time, part-time employment and informal employment. Employment status at the follow-up visit was significantly different from that at the baseline. The distributions of sociodemographic characteristics are summarized in **Table 4.1**.

### 4.1.2. Distribution of lifestyle characteristics, stratified by study period.

At the follow-up study, the proportion of current smoking decreased slightly from 6.0% to 5.2% (77/1500) with a nonsignificant increase in the proportion of former smokers from 5.6% to 7.2% (108/1500). Current smokeless tobacco use remained identical throughout the study with a proportion of 19.1% (285/1500). This variation was not significantly different. Smokeless tobacco use was described through snuff (0.2%) and chewing tobacco 18.9%. The majority of participants 58.4% currently consumed alcohol during the 5 years, but this was not statistically different. The proportion of current problematic of drinking was significantly different during the 5 years (11.6% vs 7.5%). In terms of dietary habits, the median consumption of fruits and foods rich in carbohydrates varied significantly over the 5 years. However, the median vegetable consumption was not statistically different. Median moderate-to-vigorous intensity physical activity at follow-up 3000 (IQR: 2250-3442) was significantly different from that at baseline. The rate of use and/or exposure to pesticides/insecticides was significantly increased (27.3% vs 58.2%). **Table 4.1** summarizes the distribution of lifestyle characteristics of participants by period of study.

### 4.1.3. Medical-clinical characteristics, stratified by study period.

The median BMI increased significantly from 20.4 to 20.6 kg/m² (IQR: 18.6-23.1) at the follow-up visit. The proportion of overweight participants increased significantly from baseline to final visit (8.5% vs 11.5%). Similarly, the proportion of participants with obesity increased significantly, reporting a cumulative incidence of obesity of 2.3% (34/1500). The proportion of metabolic syndrome increased significantly from 5.3% to 13.3% (200/1500).

Furthermore, the prevalence of multimorbidity at the baseline study was 19.4% (290/1500) and the cumulative incidence at the follow-up visit was 38.3% (575/1500) reporting a statistically non-significant increase in the proportion of multimorbidity. Multimorbidity rate stratified by existing chronic conditions was 13.0% (195/1500). Chronic diseases such as COPD, visual impairment and rheumatic arthritis were not studied at the baseline. The frequency of chronic diseases and the number of chronic disease association are shown in **Table 4.1**. In addition, the overall prevalence of pre-frailty and frailty was 59.3% and 8.5% (127/1500) respectively. The proportions of frailty components and the number of associations of the different components are shown in **Table 4.1** which summarizes the medical-clinical characteristics of the participants by period of study.

**Table 4.1:** Distribution of socio-demographic, lifestyle and medical-clinical characteristics of Nanoro site participants, stratified by study period; AWI-Gen study 2015-2022.

| Characteristic factors | | Baseline study N=1,500 | Follow-up study N=1,500 | P-value |
|---|---|---|---|---|
| **Socio-demographic characteristics** | | | | |
| **Age** | Age in years | 50 (45 - 55) | 55 (50 - 60) | <0.001 |
| **Age group** | Age 40 to 49 | 733 (48.9) | 339 (22.6) | - |
| | Age 50 to 59 | 712 (47.5) | 773 (51.5) | |
| | Age 60 plus | 53 (3.5) | 388 (25.9) | |
| **Gender** | Women | 786 (52.4) | 786 (52.4) | - |
| | Men | 714 (47.6) | 714 (47.6) | |
| **Ethnicity** | Mossi | 1,391 (92.9) | 1,392 (92.9) | - |
| | Gourounsi | 85 (5.7) | 85 (5.7) | |
| | Others | 21 (1.4) | 21 (1.4) | |
| **Marital status** | Single/Divorced/Separated | 13 (0.9) | 19 (1.3) | - |
| | Married/Concubinage | 1,313 (87.8) | 1,184 (79.4) | |
| | Widowed | 170 (11.4) | 288 (19.3) | |
| **Education level** | None/Non formal | 1,237 (83.0) | 1,253 (83.9) | - |
| | Primary | 177 (11.9) | 169 (11.3) | |
| | Secondary | 67 (4.5) | 60 (4.0) | |
| | Tertiary | 9 (0.6) | 11 (0.7) | |
| **Employment status** | No | 12 (0.8) | 48 (3.2) | <0.001 |
| | Yes | 1,483 (99.2) | 1,446 (96.8) | |
| **Lifestyle characteristics** | | | | |
| **Smoking status** | Never smoked | 1,322 (88.4) | 1,309 (87.6) | 0.221 |
| | Former smoker | 84 (5.6) | 108 (7.2) | |
| | Current smoker | 90 (6.0) | 77 (5.2) | |
| **Smokeless tobacco use** | Never used | 1,182 (79.8) | 1,179 (78.9) | 0.109 |
| | Former user | 10 (0.7) | 30 (2.0) | |
| | Current user | 289 (19.5) | 285 (19.1) | |
| **Alcohol consumption** | Never drink | 396 (26.52) | 415 (27.8) | 0.293 |
| | Former drinker | 134 (9.0) | 207 (13.9) | |
| | Current drinker | 963 (64.5) | 872 (58.4) | |
| **Problematic of drink** | Current non problematic | 1,324 (88.4) | 1,388 (92.5) | <0.001 |
| | Current problematic | 174 (11.6) | 112 (7.5) | |
| **Food & Dietary habits** | Fruit serving/day | 1 (1 - 2) | 0 (0 - 2) | <0.001 |
| | Vegetables serving/day | 2 (1 - 2) | 2 (1 - 2) | 0.806 |
| | Servings starchy/day | 1 (1 - 1) | 2 (2 - 3) | <0.001 |
| **Physical Activities** | MVPA (mins/week) | 2690(360 - 3360) | 3000(2250 - 3442) | <0.001 |
| **Pesticides use/exposure** | No | 1,087 (72.7) | 624 (41.8) | <0.001 |
| | Yes | 408 (27.3) | 868 (58.2) | |
| **Medical-clinical characteristics** | | | | |

| | | | | |
|---|---|---|---|---|
| **Body Mass Index** | BMI in kg/m² | 20.4 (18.6-22.7) | 20.6 (18.6-23.1) | <0.001 |
| **BMI categories** | Underweight | 362 (24.2) | 359 (23.9) | <0.001 |
| | Normal Weight | 983 (65.6) | 935 (62.3) | |
| | Overweight | 128 (8.5) | 172 (11.5) | |
| | Obesity | 25 (1.7) | 34 (2.3) | |
| **Metabolic syndrome** | No | 1,419 (94.7) | 1,300 (86.7) | <0.001 |
| | Yes | 79 (5.3) | 200 (13.3) | |
| **Blood Pressure** | Systolic Blood Pressure | 112(102.5-124.5) | 118 (107 - 131) | <0.001 |
| **Chronic diseases** | None Chronic Disease | 291 (19.4) | 294 (19.6) | 0.912 |
| | One Chronic Disease | 917 (61.2) | 631 (42.1) | |
| | Multimorbidity | 290 (19.4) | 575 (38.3) | |
| **Frequency of CD** | Cancer status | 2 (0.1) | 8 (0.5) | 0.033 |
| | Current tuberculosis | 0 (0.0) | 1 (0.1) | 0.317 |
| | Asthma | 32 (2.3) | 13 (0.9) | <0.001 |
| | Diabetes status | 47 (3.1) | 105 (7.0) | <0.001 |
| | Hypertension | 215 (14.7) | 395 (26.4) | <0.001 |
| | Cardiovascular Diseases | 19 (1.3) | 122 (8.2) | <0.001 |
| | Thyroid disease | 22 (1.5) | 69 (4.6) | <0.001 |
| | Chronic Kidney Disease | 92 (6.2) | 81 (5.5) | 0.475 |
| | Dyslipidaemia | 1,109 (75.5) | 943 (63.9) | <0.001 |
| | COPD | - | 17 (1.1) | |
| | Visual impairment | - | 21 (1.5) | |
| | Rheumatic Arthritis | - | 224 (15.0) | |
| **Chronic diseases rate** | None Chronic Disease | - | 795 (53.0) | |
| | One Chronic Disease | - | 510 (34.0) | |
| | Multimorbidity | - | 195 (13.0) | |
| **Frailty status** | Robust | - | 483 (32.2) | |
| | Pre-frail | - | 890 (59.3) | |
| | Frail | - | 127 (8.5) | |
| **Frailty components** | Weakness (grip strength) | - | 308 (20.5) | |
| | Slowness (slow walk, sec) | - | 287 (19.1) | |
| | Low activity (in min) | - | 293 (19.5) | |
| | Exhaustion | - | 344 (23.1) | |
| | Weight loss (kg/m²) | - | 359 (23.9) | |

Results are given as **medians** (IQR) or **n** (column percent).
Wilcoxon signed-rank test was performed for continuous variables.
Mac Nemar's test was performed for categorical variables
MVPA: moderate-to-vigorous intensity physical activity. BMI: body mass index
COPD: chronic obstructive pulmonary disease. CD: chronic disease.

## 4.2. Distribution of sociodemographic, lifestyle, and medical-clinical characteristics, stratified by frailty status

### 4.2.1. Distribution of sociodemographic characteristics, stratified by frailty status

In the bivariate analysis, the median age of the frail participants was 57 years (IQR: 54-62) and was significantly higher than the median age of the robust and pre-frail participants. The proportion of frail participants in the 50-59 age group was 54.3% (69/127) significantly higher. The proportion of frail women was significantly higher (61.4%) compared to that of men (38.6%). Married or cohabiting participants were 63.2% (79/127) frail while 34.4% (43/127) of frail participants had their partners deceased. Frailty was significantly the majority (92.0%) among participants with non-formal education or none education. The prevalence of frailty among unemployed participants was significantly lower (19.2%). **Table 4.2** presents the sociodemographic characteristics of robust, pre-frail, and frail participants.

### 4.2.2. Distribution of lifestyle characteristics, stratified by frailty status

The prevalence of pre-frailty and frailty among current smokers was 4.0% and 5.1% respectively and was not significantly different. Current smokeless tobacco use was significantly different in pre-frail participants compared to frail participants (20.4% vs 22.4%). The proportion of current problematic of drinking among pre-frail and frail participants was not significantly different (7.0% vs 9.4%). In terms of diet, the consumption of fruits, vegetables and carbohydrate-rich foods was significantly different among the participants. The proportion of highly active frail participants was significantly higher (68.5%). Median moderate-to-vigorous-intensity physical activity in frail participants was 1680 (IQR: 140-2790) significantly lower. Lifestyle-related characteristics of robust, pre-frail, and frail participants are summarized in **Table 4.2**.

### 4.2.3. Distribution of medical-clinical characteristics, stratified by frailty status

On the one hand, the median BMI decreased significantly and was 17.9 kg/m² (16.8-19.1) in frail participants. The prevalence of underweight among frail participants was significantly very high compared to pre-frail and robust underweight participants (68.5 vs 30.6%). Overweight and obesity were significantly very low in frail participants (6.3% vs 0.8%). On the other hand, the prevalence of multimorbidity was significantly different and was respectively 34.4% (166/483); 39.2% (349/890) and 47.2% (60/127) in robust, pre-frail, and frail participants. Similarly, the proportions

of the number of chronic diseases were significantly different among the participants of the three groups. In terms of chronic diseases, the proportion of diabetes mellitus and rheumatic arthritis were significantly different. **Table 4.2** summarizes the medical-clinical characteristics of robust, pre-frail, and frail participants.

**Table 4.2:** Distribution of sociodemographic, lifestyle, and medical-clinical characteristics, stratified by frailty status; AWI-Gen study 2015-2022.

| Characteristic factors | | Robust N=483 | Pre-frail N=890 | Frail N=127 | P-value |
|---|---|---|---|---|---|
| **Socio-demographic characteristics** | | | | | |
| **Age** | Age in years | 54 (49 - 58) | 55 (50 - 60) | 57 (54 - 62) | **<0.001** |
| **Age group** | Age 40 to 49 | 135 (28.0) | 192 (21.6) | 12 (9.4) | **<0.001** |
| | Age 50 to 59 | 253 (52.4) | 451 (50.7) | 69 (54.3) | |
| | Age 60 plus | 95 (19.7) | 247 (27.8) | 46 (36.2) | |
| **Gender** | Female | 226 (46.8) | 482 (54.2) | 78 (61.4) | **0.003** |
| | Male | 257 (53.2) | 408 (45.8) | 49 (38.6) | |
| **Ethnicity** | Mossi | 449 (93.0) | 827 (93.1) | 116 (91.3) | 0.638+ |
| | Gourounsi | 25 (5.2) | 50 (5.6) | 10 (7.9) | |
| | Others | 9 (1.9) | 11 (1.2) | 1 (0.8) | |
| **Marital status** | Unmarried/Separated | 3 (0.6) | 13 (1.5) | 3 (2.4) | **<0.001** |
| | Married/Concubinage | 418 (86.7) | 687 (77.7) | 79 (63.2) | |
| | Widowed | 61 (12.7) | 184 (20.8) | 43 (34.4) | |
| **Education level** | None/Non formal | 397 (82.2) | 741 (83.7) | 115 (92.0) | **0.002+** |
| | Primary | 72 (14.9) | 90 (10.2) | 7 (5.6) | |
| | Secondary | 11 (2.3) | 47 (5.3) | 2 (1.6) | |
| | Tertiary | 3 (0.6) | 7 (0.8) | 1 (0.8) | |
| **Employment** | No | 1 (0.2) | 23 (2.6) | 24 (19.2) | **<0.001+** |
| | Yes | 482 (99.8) | 863 (97.4) | 101 (80.8) | |
| **Lifestyle characteristics** | | | | | |
| **Smoking status** | Never smoked | 424 (87.8) | 771 (87.0) | 114 (91.2) | 0.640 |
| | Former smoker | 32 (6.6) | 70 (7.9) | 6 (4.8) | |
| | Current smoker | 27 (5.6) | 45 (5.1) | 5 (4.0) | |
| **Smokeless tobacco use** | Never used | 401 (83.0) | 689 (77.8) | 89 (71.2) | **<0.001** |
| | Former user | 6 (1.2) | 16 (1.8) | 8 (6.4) | |
| | Current user | 76 (15.7) | 181 (20.4) | 28 (22.4) | |
| **Alcohol consumption** | Never drink | 128 (26.5) | 254 (28.7) | 33 (26.4) | 0.615 |
| | Former drinker | 60 (12.4) | 128 (14.4) | 19 (15.2) | |
| | Current drinker | 295 (61.1) | 504 (56.9) | 73 (58.4) | |
| **Problematic of drink** | Current non problematic | 445 (92.1) | 828 (93.0) | 115 (90.6) | 0.560 |
| | Current problematic | 38 (7.9) | 62 (7.0) | 12 (9.4) | |
| **Dietary habits** | Fruit serving/day | 1 (0 - 2) | 0 (0 - 2) | 0 (0 - 1) | **<0.001** |

| | | | | | |
|---|---|---|---|---|---|
| | Vegetables serving/day | 2 (1 - 2) | 2 (1 - 2) | 1 (0 - 2) | **<0.001** |
| **Carbohydrate-rich foods** | Servings starchy/day | 2 (2 - 3) | 2 (2 - 3) | 2 (2 - 2) | **0.037** |
| **Physical Activities** | MVPA (mins/week) | 3240(2880-3720) | 2935(2100-3360) | 1680(140-2790) | **<0.001** |
| **MVPA (METs/week)** | Low activity/Inactivity | 0 (0.0) | 92 (10.3) | 32 (25.2) | **<0.001+** |
| | Moderately active | 0 (0.0) | 19 (2.1) | 8 (6.3) | |
| | Highly active | 483 (100.0) | 779 (87.5) | 87 (68.5) | |
| **Pesticides use/exposure** | No | 187 (38.7) | 381 (43.1) | 56 (45.2) | 0.220 |
| | Yes | 296 (61.3) | 504 (56.9) | 68 (54.8) | |
| **Medical-clinical characteristics** | | | | | |
| **Body Mass Index** | BMI in kg/m² | 21.4 (20.0-23.6) | 20.3 (18.1-23.1) | 17.9(16.8-19.1) | **<0.001** |
| **BMI categories** | Underweight | 0 (0.0) | 272 (30.6) | 87 (68.5) | **<0.001+** |
| | Normal Weight | 409 (84.7) | 495 (55.6) | 31 (24.4) | |
| | Overweight | 64 (13.3) | 100 (11.2) | 8 (6.3) | |
| | Obesity | 10 (2.1) | 23 (2.6) | 1 (0.8) | |
| **Metabolic syndrome** | No | 420 (87.0) | 769 (86.4) | 111 (87.4) | 0.930 |
| | Yes | 63 (13.0) | 121 (13.6) | 16 (12.6) | |
| **Chronic diseases** | None Chronic Disease | 111 (23.0) | 159 (17.9) | 24 (18.9) | **0.024** |
| | One Chronic Disease | 206 (42.7) | 382 (42.9) | 43 (33.9) | |
| | Multimorbidity | 166 (34.4) | 349 (39.2) | 60 (47.2) | |
| **Frequency of CD** | Cancer status | 2 (0.4) | 6 (0.7) | 0 (0.0) | 0.857+ |
| | Current tuberculosis | 0 (0.0) | 1 (0.1) | 0 (0.0) | <0.999+ |
| | Asthma | 3 (0.6) | 9 (1.0) | 1 (0.8) | 0.830+ |
| | COPD | 5 (1.0) | 9 (1.0) | 3 (2.4) | 0.322+ |
| | Visual impairment | 5 (1.1) | 12 (1.4) | 4 (3.4) | 0.178+ |
| | Diabetes status | 22 (4.6) | 69 (7.8) | 14 (11.0) | **0.015** |
| | Hypertension | 119 (24.6) | 245 (27.7) | 31 (24.6) | 0.421 |
| | CVD | 31 (6.4) | 83 (9.4) | 8 (6.6) | 0.120 |
| | Thyroid disease | 23 (4.8) | 42 (4.8) | 4 (3.2) | 0.740 |
| | CKD | 21 (4.4) | 53 (6.0) | 7 (5.7) | 0.433 |
| | Rheumatic Arthritis | 63 (13.0) | 131 (14.8) | 30 (24.2) | **0.008** |
| | Dyslipidaemia | 289 (59.8) | 572 (64.3) | 82 (65.1) | 0.224 |

Results are given as **medians** (IQR) or **n** (column percent).
Kruskal Wallis test was performed for continuous variables when the conditions were met.
Pearson Chi-Square's test was performed for categorical variables.
+ Fisher's Exact test was performed when the conditions were met.
MVPA: moderate-to-vigorous intensity physical activity. METs: Metabolic Equivalents
BMI: body mass index. CD: chronic disease. CVD: cardiovascular disease.
COPD: chronic obstructive pulmonary disease. CKD: chronic kidney disease.

## 4.3. Distribution of sociodemographic, lifestyle, and medical-clinical characteristics, stratified by chronic diseases status

### 4.3.1. Distribution of sociodemographic characteristics, stratified by chronic diseases status

In the bivariate analysis, the median age of participants with multimorbidity was 55 years (IQR: 51-60) while the median age of participants with none chronic disease was the highest (56) compared to other medians. Similarly, the proportion of the 50-59 age group among participants with multimorbidity was the highest (51.3%). However, the distribution of this age difference was marginally significant. The proportion of women with multimorbidity was significantly higher (59.0%) compared to that of men (41.0%). Married or cohabiting participants were in 75.2% with multimorbidity while 24.3% of participants with multimorbidity had their partners deceased. This difference in the proportion of marital status was statistically significant. Multimorbidity was predominant (82.0%) in participants with none level of education, but this difference was not statistically significant. The prevalence of multimorbidity among employed participants was significantly higher (95.5%). The sociodemographic characteristics of participants without chronic disease, with one chronic disease and with multimorbidity are summarized in **Table 4.3**.

### 4.3.2. Distribution of lifestyle characteristics, stratified by chronic diseases status

Among current smokers, the prevalence of multimorbidity was 3.5% (20/575) and was significantly lower. Current smokeless tobacco use was slightly different among participants with multimorbidity (18.6% vs 21.1%), but this slight difference was marginally significant. Current alcohol consumption among participants with multimorbidity was significantly higher 50.9% (292/575). The proportion of current problematic of drinking among participants with multimorbidity was significantly different (5.7% vs 6.7%). From a dietary point of view, the consumption of fruits, vegetables and carbohydrate-rich foods was not significantly different. The prevalence of participants with multimorbidity and highly active was higher (87.5%), but this difference was not statistically significant. Median MVPA in participants with multimorbidity was 2940 (IQR: 1980-3360) significantly lower compared to other groups of participants. Use and/or exposure to pesticides/insecticides was significantly higher in participants with multimorbidity (53.4%). **Table 4.3** summarizes lifestyle characteristics of participants without chronic disease, with one chronic disease, or with multimorbidity.

### 4.3.3. Distribution of clinical characteristics, stratified by chronic diseases status

On the one hand, the median BMI increased significantly and was 21.5 kg/m² (19.0-24.8) in participants with multimorbidity. The prevalence of obesity and overweight among participants with multimorbidity was significantly different and was 4.3% and 19.7%, respectively. The prevalence of metabolic syndrome was significantly higher in participants with multimorbidity compared to the other groups (26.3% vs 7.4). On the other hand, the prevalence of pre-frailty and frailty in participants with multimorbidity was significantly different and was respectively 60.7% (349/575) and 10.4% (60/575). Similarly, the proportions of the number of frailty components were significantly different among the participants. The medical-clinical characteristics of participants in the three groups of chronic conditions are summarized in **Table 4.3**.

**Table 4.3:** Distribution of sociodemographic, lifestyle, and medical-clinical characteristics, stratified by chronic diseases status; AWI-Gen study 2015-2022.

| Characteristic factors | | None Chronic Disease N=294 | One Chronic Disease N=631 | Multimorbidity N=575 | P-value |
|---|---|---|---|---|---|
| **Socio-demographic characteristics** | | | | | |
| **Age** | Age in years | 56 (50 - 59) | 54 (49 - 59) | 55 (51 - 60) | 0.090 |
| **Age group** | Age 40 to 49 | 69 (23.5) | 158 (25.0) | 112 (19.5) | 0.066 |
| | Age 50 to 59 | 158 (53.7) | 320 (50.7) | 295 (51.3) | |
| | Age 60 plus | 67 (22.8) | 153 (24.2) | 168 (29.2) | |
| **Gender** | Female | 100 (34.0) | 347 (55.0) | 339 (59.0) | **<0.001** |
| | Male | 194 (66.0) | 284 (45.0) | 236 (41.0) | |
| **Ethnicity** | Mossi | 281 (95.6) | 589 (93.3) | 522 (91.1) | 0.058+ |
| | Gourounsi | 10 (3.4) | 37 (5.9) | 38 (6.6) | |
| | Others | 3 (1.0) | 5 (0.8) | 13 (2.3) | |
| **Marital status** | Unmarried/Separated | 7 (2.4) | 9 (1.4) | 3 (0.5) | **<0.001+** |
| | Married/Concubinage | 254 (87.3) | 499 (79.6) | 431 (75.2) | |
| | Widowed | 30 (10.3) | 119 (19.0) | 139 (24.3) | |
| **Education level** | None/Non formal | 236 (81.1) | 547 (87.0) | 470 (82.0) | 0.098+ |
| | Primary | 40 (13.7) | 61 (9.7) | 68 (11.9) | |
| | Secondary | 12 (4.1) | 19 (3.0) | 29 (5.1) | |
| | Tertiary | 3 (1.0) | 2 (0.3) | 6 (1.0) | |
| **Employment** | No | 4 (1.4) | 18 (2.9) | 26 (4.5) | **0.035+** |
| | Yes | 287 (98.6) | 611 (97.1) | 548 (95.5) | |
| **Lifestyle characteristics** | | | | | |
| **Smoking status** | Never smoked | 232 (79.7) | 566 (90.0) | 511 (89.0) | **<0.001** |
| | Former smoker | 30 (10.3) | 35 (5.6) | 43 (7.5) | |
| | Current smoker | 29 (10.0) | 28 (4.5) | 20 (3.5) | |

| | | | | | |
|---|---|---|---|---|---|
| **Smokeless tobacco use** | Never used | 238 (81.8) | 505 (80.3) | 436 (76.0) | 0.067 |
| | Former user | 6 (2.1) | 7 (1.1) | 17 (3.0) | |
| | Current user | 47 (16.2) | 117 (18.6) | 121 (21.1) | |
| **Alcohol consumption** | Never drink | 52 (17.9) | 171 (27.2) | 192 (33.4) | **<0.001** |
| | Former drinker | 30 (10.3) | 87 (13.8) | 90 (15.7) | |
| | Current drinker | 209 (71.8) | 371 (59.0) | 292 (50.9) | |
| **Problematic of drink** | Current non problematic | 257 (87.4) | 589 (93.3) | 542 (94.3) | **<0.001** |
| | Current problematic | 37 (12.6) | 42 (6.7) | 33 (5.7) | |
| **Dietary habits** | Fruit serving/day | 0 (0 - 2) | 0 (0 - 2) | 0 (0 - 2) | 0.997 |
| | Vegetables serving/day | 2 (1 - 2) | 2 (1 - 2) | 2 (1 - 2) | 0.054 |
| **Carbohydrate-rich foods** | Servings starchy/day | 2 (2 - 3) | 2 (2 - 3) | 2 (2 - 3) | 0.104 |
| **Physical Activities** | MVPA (mins/week) | 3060(2400-3510) | 3060(2450-3450) | 2940(1980-3360) | **0.007** |
| **MVPA (METs/week)** | Low activity/Inactivity | 21 (7.1) | 43 (6.8) | 60 (10.4) | 0.177+ |
| | Moderately active | 4 (1.4) | 11 (1.7) | 12 (2.1) | |
| | Highly active | 269 (91.5) | 577 (91.5) | 503 (87.5) | |
| **Pesticides use /exposure** | No | 115 (39.7) | 242 (38.5) | 267 (46.6) | **0.012** |
| | Yes | 175 (60.3) | 387 (61.5) | 306 (53.4) | |
| **Medical-clinical characteristics** | | | | | |
| **Body Mass Index** | BMI in kg/m² | 19.9 (18.1-21.8) | 20.3(18.5-22.6) | 21.5(19.0-24.8) | **<0.001** |
| **BMI categories** | Underweight | 89 (30.3) | 156 (24.7) | 114 (19.8) | **<0.001** |
| | Normal Weight | 185 (62.9) | 427 (67.7) | 323 (56.2) | |
| | Overweight | 16 (5.4) | 43 (6.8) | 113 (19.7) | |
| | Obesity | 4 (1.4) | 5 (0.8) | 25 (4.3) | |
| **Metabolic syndrome** | No | 292 (99.3) | 584 (92.6) | 424 (73.7) | **<0.001+** |
| | Yes | 2 (0.7) | 47 (7.4) | 151 (26.3) | |
| **Frailty status** | Robust | 111 (37.8) | 206 (32.7) | 166 (28.9) | **0.024** |
| | Pre-frail | 159 (54.1) | 382 (60.5) | 349 (60.7) | |
| | Frail | 24 (8.2) | 43 (6.8) | 60 (10.4) | |

Results are given as **medians** (IQR) or **n** (column percent).
Kruskal Wallis test was performed for continuous variables when the conditions were met.
Pearson Chi-Square's test was performed for categorical variables.
+ Fisher's Exact test was performed when the conditions were met.
MVPA: moderate-to-vigorous intensity physical activity. METs: Metabolic Equivalents
BMI: body mass index. CD: chronic disease. CVD: cardiovascular disease.
COPD: chronic obstructive pulmonary disease. CKD: chronic kidney disease.

## 4.4. Analysis of factors associated with frailty

### 4.4.1. Analysis of socio-demographic factors associated with frailty

In univariate analysis age, gender, marital status, education level and employment status were significantly associated with frailty. In multivariate analysis, gender and participant education were

no longer significantly associated with frailty after adjusting for the effect of other covariates. Being 50 to 59 years old and over 60 years old were significantly associated with increased odds of frailty with respective aOR of 1.4 and 1.6. Similarly, having a deceased partner was significantly associated with increased odds of 50% risk of frailty with aOR of 1.5. For being unemployed, the odds of being frail versus pre-frail and robust was 2.5 times greater. **Table 4.4** summarizes the socio-demographic factors associated with frailty.

### 4.4.2. Analysis of lifestyle factors associated with frailty

In univariate analysis, smoking status, alcohol consumption, carbohydrate-rich food consumption, and pesticide exposure and/or use were not associated with frailty. Furthermore, after adjustment of the other covariates in the multivariate analysis, smokeless tobacco use, the consumption of fruits and vegetables and physical activities remained significantly associated with frailty. Having been a former user of smokeless tobacco was associated with 150% increased odds of frailty (aOR 2.5). However, for any increase in the consumption of fruit and vegetables servings, the risk of being frail decreased on average by 10% and 10% respectively (aOR 0.9). Being highly active was significantly associated with reduced odds of 90% of being frail (aOR 0.1). **Table 4.4** summarizes lifestyle factors associated with frailty.

### 4.4.3. Analysis of medical-clinical factors associated with frailty

Body mass index, multimorbidity, diabetes mellitus and rheumatic arthritis were significantly the factorial variables associated with frailty in the univariate analysis. Only BMI and multimorbidity remained significantly associated with frailty in the multivariate model. The odds of being frail versus pre-frail was 26.2 times greater on average for being underweight. Similarly, having multimorbidity was 1.4 more likely to be frail versus pre-frail. **Table 4.4** summarizes the medical-clinical factors associated with frailty.

**Table 4.4:** Multivariate ordinal logistic regression analysis of socio-demographic, lifestyle, and medical-clinical factors associated with frailty; AWI-Gen study 2015-2022.

| Associated risk factors | | OR (95%CI) | P-value | aOR (95%CI) | P-value |
|---|---|---|---|---|---|
| **Socio-demographic determinants** | | | | | |
| **Age group** | Age 40 to 49 | Ref | | Ref | |
| | Age 50 to 59 | 1.5 (1.1-1.9) | 0.002 | 1.4 (1.0-1.9) | **0.012** |
| | Age 60 plus | 2.2 (1.6-2.9) | <0.001 | 1.6 (1.1-2.2) | **0.008** |
| **Gender** | Female | 1.4 (1.2-1.7) | <0.001 | 1.1 (0.8-1.5) | 0.447 |
| | Male | Ref | | Ref | |
| **Marital status** | Unmarried/Separated | 2.7 (1.1-6.9) | 0.036 | 2.0 (0.7-5.6) | 0.178 |
| | Married/Concubinage | Ref | | Ref | |
| | Widowed | 2.2 (1.7-2.8) | <0.001 | 1.5 (1.1-2.1) | **0.009** |
| **Education level** | None/Non formal | Ref | | Ref | |
| | Primary | 0.6 (0.4-0.8) | 0.001 | 0.8 (0.6-1.2) | 0.390 |
| | Secondary | 1.4 (0.8-2.2) | 0.236 | 1.4 (0.7-2.6) | 0.278 |
| | Tertiary | 1.2 (0.4-3.9) | 0.794 | 1.7 (0.4-7.0) | 0.466 |
| **Employment** | No | 13.8 (7.7-24.8) | <0.001 | 2.5 (1.1-5.8) | **0.032** |
| | Yes | Ref | | Ref | |
| **Lifestyle determinants** | | | | | |
| **Smokeless tobacco use** | Never used | Ref | | Ref | |
| | Former user | 3.2 (1.5-7.0) | 0.003 | 2.5 (1.1-5.7) | **0.033** |
| | Current user | 1.4 (1.1-1.8) | 0.013 | 0.8 (0.6-1.1) | 0.214 |
| **Dietary habits** | Fruit serving/day | 0.9 (0.8-0.9) | <0.001 | 0.9 (0.8-1.0) | **0.042** |
| | Vegetables serving/day | 0.9 (0.8-0.9) | <0.001 | 0.9 (0.8-1.0) | **0.036** |
| **Physical Activities** | Low activity/Inactivity | 0.9 (0.4-2.0) | 0.742 | 0.7 (0.2-2.3) | 0.612 |
| | Moderately active | Ref | | Ref | |
| | Highly active | 0.1 (0.1-0.3) | <0.001 | 0.1 (0.0-0.2) | **<0.001** |
| **Medical-clinical determinants** | | | | | |
| **Body Mass Index** | Underweight | 17.9 (12.4-25.7) | <0.001 | 26.2 (17.1-40.2) | **<0.001** |
| | Normal Weight | Ref | | Ref | |
| | Overweight | 1.3 (1.0-1.9) | 0.082 | 1.1 (0.7-1.5) | 0.698 |
| | Obesity | 1.8 (0.9-3.6) | 0.118 | 1.2 (0.5-2.5) | 0.699 |
| **Chronic diseases** | None Chronic Disease | Ref | | Ref | |
| | One Chronic Disease | 1.2 (0.9-1.5) | 0.281 | 1.3 (0.9-1.7) | 0.124 |
| | Multimorbidity | 1.5 (1.1-2.0) | 0.007 | 1.4 (1.0-2.1) | **0.037** |
| **Frequency of CD** | Diabetes status | 1.8 (1.2-2.7) | 0.004 | 1.4 (0.8-2.3) | 0.144 |
| | Rheumatic Arthritis | 1.4 (1.1-2.0) | 0.017 | 1.3 (0.9-1.9) | 0.101 |

CD: chronic disease.
CI: Confidence interval. OR: odds ratio. aOR: adjusted odds ratio.

## 4.5. Analysis of factors associated with multimorbidity

### 4.5.1. Analysis of socio-demographic factors associated with multimorbidity

Education level was not significantly associated with multimorbidity versus none chronic disease in the multivariate analysis after adjusting for the other covariates. However, being over 60 years old; being a woman; having a deceased partner and being unemployed were significantly associated with increased relative risk ratio of multimorbidity versus none chronic disease. Being a woman was associated with a high relative risk ratio of 110% for having a chronic disease and 160% for having multimorbidity. The risk of having a chronic disease or multimorbidity among unemployed participants was 4.5 identically high in both groups. **Table 4.5** summarizes the sociodemographic factors associated with multimorbidity.

### 4.5.2. Analysis of lifestyle factors associated with multimorbidity

Current smoking status, smokeless tobacco use, vegetable and carbohydrate-rich foods consumption, and pesticide exposure and/or use were not significantly associated with multimorbidity versus none chronic disease. Similarly, being active was not significantly associated with multimorbidity. However, alcohol consumption and fruit consumption were remained significantly associated with multimorbidity. Being a current alcohol consumer was associated with a 60% reduced risk of multimorbidity (RRR 0.4). The relative risk ratio of having multimorbidity versus none chronic disease decreased on average by 10% for every increase in fruit serving consumption (RRR 0.9). **Table 4.5** summarizes lifestyle factors associated with multimorbidity.

### 4.5.3. Analysis of medical-clinical factors associated with multimorbidity

Body mass index and frailty were significantly associated with multimorbidity versus none chronic disease. Overweight participants were 5.0 more likely to have multimorbidity compared to normal weight participants. Having obesity was more likely to have increased relative risk ratio of multimorbidity (RRR 3.4). The risk of having multimorbidity was 1.8 and 2.1 times higher for pre-frail and frail participants respectively. **Table 4.5** summarizes the medical-clinical factors associated with multimorbidity.

**Table 4.5:** Multivariate multinomial logistic regression analysis of socio-demographic, lifestyle, and medical-clinical factors associated with multimorbidity; AWI-Gen study 2015-2022.

| Associated risk factors | | None CD vs One CD | | None CD vs Multimorbidity | |
|---|---|---|---|---|---|
| | | **RRR (95%CI)** | **P-value** | **RRR (95%CI)** | **P-value** |
| **Socio-demographic determinants** | | | | | |
| **Age group** | Age 40 to 49 | Ref | | Ref | |
| | Age 50 to 59 | 0.8 (0.5-1.1) | 0.218 | 1.1 (0.8-1.7) | 0.557 |
| | Age 60 plus | 1.0 (0.6-1.5) | 0.894 | 1.8 (1.1-2.8) | **0.019** |
| **Gender** | Female | 2.1 (1.4-3.0) | **<0.001** | 2.6 (1.7-3.9) | **<0.001** |
| | Male | Ref | | Ref | |
| **Marital status** | Unmarried/Separated | 0.9 (0.3-3.0) | 0.896 | 0.3 (0.1-1.5) | 0.157 |
| | Married/Concubinage | Ref | | Ref | |
| | Widowed | 1.3 (0.8-2.1) | 0.300 | 1.6 (1.0-2.7) | **0.050** |
| **Education level** | None/Non formal | Ref | | Ref | |
| | Primary | 0.9 (0.6-1.5) | 0.799 | 1.2 (0.7-2.0) | 0.446 |
| | Secondary | 0.9 (0.4-2.1) | 0.874 | 0.9 (0.4-2.2) | 0.877 |
| | Tertiary | 0.4 (0.1-2.8) | 0.344 | 1.4 (0.3-7.9) | 0.673 |
| **Employment** | No | 4.5 (1.1-18.5) | **0.034** | 4.5 (1.1-18.0) | **0.036** |
| | Yes | Ref | | Ref | |
| **Lifestyle determinants** | | | | | |
| **Smoking status** | Never smoked | Ref | | Ref | |
| | Former smoker | 0.7 (0.4-1.2) | 0.175 | 0.9 (0.5-1.6) | 0.817 |
| | Current smoker | 0.6 (0.3-1.1) | 0.116 | 0.7 (0.4-1.4) | 0.358 |
| **Smokeless tobacco use** | Never used | Ref | | Ref | |
| | Former user | 0.3 (0.1-1.1) | 0.068 | 0.8 (0.3-2.2) | 0.603 |
| | Current user | 0.8 (0.5-1.2) | 0.272 | 1.0 (0.7-1.6) | 0.935 |
| **Alcohol consumption** | Never drink | Ref | | | |
| | Former drinker | 0.8 (0.5-1.4) | 0.472 | 0.7 (0.4-1.3) | 0.277 |
| | Current drinker | 0.6 (0.4-0.9) | **0.014** | 0.4 (0.3-0.6) | **<0.001** |
| **Dietary habits** | Fruit serving/day | 0.9 (0.9-1.1) | 0.382 | 0.9 (0.8-1.0) | **0.015** |
| | Vegetables serving/day | 0.9 (0.9-1.1) | 0.540 | 1.1 (0.9-1.2) | 0.233 |
| **Physical Activities** | Low activity/Inactivity | 1.5 (0.4-6.0) | 0.538 | 1.5 (0.4-6.1) | 0.534 |
| | Moderately active | Ref | | Ref | |
| | Highly active | 1.1 (0.6-2.3) | 0.712 | 1.2 (0.6-2.4) | 0.665 |
| **Medical-clinical determinants** | | | | | |
| **Body Mass Index** | Underweight | 0.6 (0.4-0.8) | **0.004** | 0.4 (0.3-0.6) | **<0.001** |
| | Normal Weight | Ref | | Ref | |
| | Overweight | 1.3 (0.7-2.5) | 0.369 | 5.0 (2.8-9.1) | **<0.001** |
| | Obesity | 0.5 (0.1-2.1) | 0.363 | 3.4 (1.1-11.0) | **0.041** |
| **Frailty status** | Robust | Ref | | Ref | |
| | Pre-frail | 1.5 (1.1-2.2) | **0.015** | 1.8 (1.2-2.6) | **0.002** |
| | Frail | 1.1 (0.5-2.1) | 0.872 | 2.1 (1.0-4.2) | **0.039** |

CD: chronic disease. CI: Confidence interval. RRR: relative risk ratio.

# CHAPTER 5: DISCUSSION

This chapter describes the interpretation of key findings on factors associated with frailty and multimorbidity in middle-aged adults. The research question is answered through the synthesis of the main results whose interpretations have been supported by previous studies. Likewise, the clinical relevance of the results of this study was described as well as the strengths and limitations of the study. In addition, recommendations based on the main findings have been formulated following the conclusion of this chapter.

## 5.1. Main findings

In a rural population cohort of 1500 participants followed over the period 2015-2022 in Burkina Faso, we determined risk factors associated with frailty and multimorbidity among middle-aged adults from 40 to 65 years old. Our findings show that the prevalence of pre-frailty and frailty was 59.3% and 8.5% respectively. Similarly, the prevalence of multimorbidity was 38.3%. Among the frailty phenotypic criteria, weight loss (23.9%) and self-reported exhaustion (23.1%) were the most frequently observed criteria. As for the twelve chronic diseases, dyslipidemia (63.9%), hypertension (26.4%), and rheumatic arthritis (15.0%) were the most reported. On the one hand, increasing age (≥ 50 years), having a deceased partner, being unemployed, smokeless tobacco use, underweight and multimorbidity were independently and strongly associated with higher odds of frailty. Nevertheless, the increased consumption of fruit and vegetable servings and being highly active significantly reduced the odds of frailty. On the other hand, the increased risk of multimorbidity compared to the absence of chronic disease was strongly associated with increasing age (≥ 60 years), being a woman, having a deceased partner, being unemployed, being overweight, being obese, pre-frailty and frailty. However, current alcohol consumption, and increased consumption of fruit servings independently reduced the increased risk of multimorbidity.

### 5.1.1. Sociodemographic determinants of frailty and multimorbidity

Half of the population was aged 55, while a quarter of this population was aged 60 to 65. This proves that this population was made up of middle-aged adults categorized by the age group ranging from 40 to 65 years old. This observation is similar to a study conducted in a rural setting of Burkina Faso (26,27). However, most studies on frailty and multimorbidity have been conducted in people over 60 (28,43,84). In addition, the population was mostly married and uneducated

(80%), and was composed of a majority of women (52.4%). These findings are consistent with the results of the general census of the population of Burkina in 2020 (30). In addition, participants had been employed in almost all cases at the baseline study while at the follow-up study, this proportion was significantly reduced from 96% of cases. This implies that some participants have lost their jobs due to total disability, retirement or some other illness. Moreover, the observation of these socio-demographic characteristics could be explained by the character of the rural site of the study where the majority of the participants are exposed to poverty, carry out agricultural activities and are uneducated compared to the urban environment. In view of these observations reported, additional longitudinal studies of stratification by zone are necessary.

In this study, half of the participants aged 50 to 59 were frail and had multimorbidity (54.3% vs 51.3%) while more than a third of this frail population (36.2%) was over 60 years old, and had multimorbidity (29.2%). Increasing age was strongly associated with frailty and multimorbidity. Indeed, participants aged 50 to 59 and over 60 had a respective increase of 40% and 60% in the odds of developing frailty. As for multimorbidity compared to the absence of a chronic disease, only participants over the age of 60 had an 80% increase in the relative risk of developing the condition. Our findings support evidence of the aging process involved in frailty and multimorbidity through the mechanism of homeostatic dysregulation, where the increase in interleukin (IL-6) has been identified as a targeted biomarker to detect chronic diseases in the elderly (72,75,76). Furthermore, the evidence for this causal association that comes from Fried's original study is supported by our results (9). Our findings are also similar to the various conclusions reported in many studies conducted in SSA where frailty and multimorbidity commonly occur with aging (9,18,21,26,33,55). Indeed, in the pilot study conducted by Fried et al, frailty was 6.9% and increased with age over 60 years. In studies conducted in South Africa and Burkina Faso, the proportions of frailty (5.4 to 13.2%) increased with age over 60 years. As for multimorbidity, increasing age over 60 years increased the risk of developing chronic diseases causing multimorbidity. Moreover, our finding supports the hypothesis of the occurrence of frailty and multimorbidity in middle-aged adults aged 40-65 years. It would be advisable to systematically identify people aged over 50 to establish prospects for prevention. The different approaches to aging should be considered for a better understanding of the heterogeneity of health states in the elderly. Geriatric medicine appears as a second approach that considers the assessment of the state

through the biological mechanism of diseases. Thus, new therapeutic approaches targeting the molecular mechanisms involved in frailty and multimorbidity offer the possibility of slowing down the aging process.

Frailty and multimorbidity were more frequently observed in women compared to men in almost two-thirds of cases. The positive association between gender and frailty was only significant on univariate analysis. Therefore, this study was unable to support the evidence for the association between gender and frailty reported in many studies where the odds of female frailty is high (9,13,21,26). Female gender is a major determinant and the susceptibility for females to cross the frailty threshold is higher due to lean body mass and low strength compared to males of the same age (9). In addition, the effect of aging combined with this thinness and weakness will probably contribute to the occurrence of frailty (72,75,76). The lack of evidence in this study could be related to the method of selection and processing of participant information. However, being a woman was strongly associated with multimorbidity compared to the absence of chronic disease. The risk of developing multimorbidity in women was 1.6 greater than the risk in men. Our analyses corroborate this association documented in numerous studies in SSA (18,27,33,84). The main reason for this association is related to the intrinsic risk of multimorbidity in women (5). However, this causal association could possibly be related to differences in genetically acquired risk, hormonal differences, and sex differences in behaviours (5,6). Furthermore, inadequate nutritional intake and loneliness are the main extrinsic effects of sarcopenia that illustrate the vulnerability of frailty and multimorbidity in older women (9,69). Therefore, screening, detection, treatment, and prevention of frailty and multimorbidity must be much more oriented in women. Similarly, a dietary supplement is an initiative to prevent thinness and weak strength in women.

Participants who had their spouses deceased were frail in a third of cases (34.4%) while multimorbidity was present in this group in a quarter of cases (24.3%). In addition, having a deceased partner was positively associated with a 50% increased odds of frailty risk. Similarly, the risk of multimorbidity among participants who had a deceased partner was 60% greater than the risk among other participants. Our findings support the demonstration of the causal association between marital status and frailty on the one hand (26,77), and between marital status and multimorbidity on the other hand, confirmed by numerous studies (33,84). Also, our results are

similar to the conclusions of the studies carried out in SSA (59,82,83), and more particularly in rural setting of Burkina (26,27). The consequence of having a deceased partner exposes you to growing loneliness and stress that induces chronic oxidation at the base of premature aging (71–73). In addition, having a deceased partner in rural areas reflects a reduction in support for activities and exposes you to growing poverty. The exposure of a frail person to a stressful factor such as the onset of a chronic disease or the death of a partner increases the susceptibility of precipitation into disability (71–73). Therefore, it is important to recognize frailty and multimorbidity as disabling conditions and to consider early intervention measures to reverse and delay certain evolutionary aspects.

The prevalence of frailty and multimorbidity among unemployed participants was significantly low (19.2% and 4.5%). Being unemployed, the odds of being frail compared to pre-frail and robust was 2.5 times higher. The risk of having a chronic disease or multimorbidity among unemployed participants was 4.5 times higher in both groups. The discovery of this result confirms the causal association established in previous studies (9,33,34,77,84). Moreover, our conclusions are consistent with the conclusions of studies conducted in SSA where the lowest wealth quintile of socioeconomic status was identified as predisposing factors (23,26,33). However, there is a discrepancy in findings reported in the literature where some authors have argued that having a high socio-economic status puts one at risk of developing frailty or multimorbidity (27,82,85). Individuals with a high socio-economic status have in most cases the necessary resources for their adequate care. As a result, the onset and progression of frailty and multimorbidity in this population group is relatively delayed. The management of frailty and multimorbidity should be optimized through a multisectoral approach among people who are unemployed or have a low socioeconomic status. Similarly, management strategies and resource allocation must be optimally targeted to the most vulnerable people. Moreover, further studies are needed to better establish the direction of the causal association.

### 5.1.2. Lifestyle determinants of frailty and multimorbidity

The lifestyle description of follow-up study participants consisted of a non-significant decrease in current smokers at 5.2%, while current smokeless tobacco consumption remained constant at 19.1% throughout the study. Current alcohol consumption was predominant during the 5 years of

follow-up (58.4%) with a significantly different alcohol consumption problematic. These observations are consistent with the findings of a national STEPS survey conducted in 2021 where the prevalence of smoking among middle-aged adults was 9.1% and that of alcohol consumption was 35.9% (96). Moreover, our results are supported by the conclusions of a study carried out by Boua et al., in four countries of SSA where in Burkina Faso the prevalence of current smoking was 6.0% and that of current alcohol consumption was 64.5% (97). The low proportion reported would be linked to the rural nature of the study site. The total duration of physical activities was significantly increased. This finding supports the results of the baseline study (98). The increase in the total duration of the activities would probably be related to the recruitment periods which influence the activities of the participants. Awareness initiatives were to be deployed to influence lifestyle of participants on smoking, tobacco consumption, alcoholism, and physical activity. The adoption of a healthy lifestyle remains a suitable long-term intervention for reducing the risks of frailty and multimorbidity.

Frailty was not significantly observed in current smokers while multimorbidity was only positively observed in these participants in the univariate analysis. Thus, we were unable to demonstrate the link of association of smoking status with frailty and with multimorbidity to confirm the conclusions of previous studies (34,77,99). Similarly, in the literature of SSA countries, the link of the association between frailty and smoking status has been rarely reported despite the contribution of many research works on frailty (21,26,43,82,85). Furthermore, the link of association of multimorbidity and smoking status has been documented in SSA (82,85). Former users of smokeless tobacco had a 150% increased risk of developing frailty. This demonstration corroborates the evidence of the link of the causal association and is consistent with the conclusions of previous studies (99). In SSA, not having smoked has been identified as a factor that may limit the occurrence of multimorbidity (82,85). The absence of evidence of the effect of smoking status in the present study could probably be linked to a set of confounding factors that may have escaped the methodology of inclusion of numbers and analysis. It could also be an error in the evaluation of consumption habits made by the participant. However, the evidence for the causal association remains strong and smoking status remains a major determinant due to its detrimental actions (34,77,99). Indeed, the chemicals in cigarette or tobacco smoke leads to chronic inflammation, the long-term consequences of which result from muscle wasting and accelerated aging (34,77,99).

Awareness of the harmful effects of smoking must be reinforced to reduce the risks associated with frailty and multimorbidity. In addition, not smoking or not using tobacco increases the possibility of preventing and reducing NCDs.

Contrary to the hypothesis of a causal association, current alcohol users had a 60% reduction in risk of multimorbidity compared to other participants. This supports the conclusions of a study conducted by Rifqah et al., in South Africa, where the effect of current alcohol consumption was protective in the development of multimorbidity (23). There are many discrepancies on the evidence of the link and the type of association between alcohol consumption and frailty on the one hand (34,77), between alcohol consumption and multimorbidity on the other (59,82). However, if the evaluation of the association link remains controversial, the long-term effects should not be ignored. The uncertainty of this association could probably be due to errors in the assessment of consumption habits reported by the participants. Moreover, it seems plausible that a number of confounding factors attempt to elucidate this very unexpected association. Additional longitudinal studies are needed to clarify the meaning of the causal relationship and for a targeted reorientation of prevention strategies on alcohol consumption.

Any increase in the consumption of vegetables and fruit servings significantly reduced the risk of frailty and multimorbidity by 10% on average. This demonstration supports the hypothesis of a protective association of vegetable and fruit consumption in the development of frailty (38). Our findings are similar to findings reported by previous studies (38,57). This also confirms the protective role of fruits in the development of multimorbidity (33,82), while the demonstration of the protective effect of vegetables remains unconfirmed in this study, unlike previous studies (86). Moreover, our conclusions are consistent with the conclusions of previous studies conducted in SSA (57,82). The main explanation that demonstrates the protective effect of fruits and vegetables is linked to their composition of micronutrients such as vitamin compounds that are mainly involved in the functioning of the immune system. This is why community initiatives must be developed to reinforce the daily consumption of at least 5 servings of fruits and vegetables as recommended by WHO. Similarly, vitamin supplementation combined with increased consumption of fruit and vegetable servings can be considered to reduce or prevent frailty and

multimorbidity. In addition, community initiatives should also strengthen the promotion of healthy diets and lifestyles conducive to health.

Being highly active was significantly associated with 90% reduced odds of being frail. This finding supports the findings of previous studies on the protective effect of physical activity in reducing and preventing frailty (36). Indeed, studies have widely supported that physical activities in the form of resistance exercises have a beneficial role in preventing and treating the risk of frailty unlike the physical inactivity which increases the risk of developing frailty (36). As for the evidence of the association between physical activity and multimorbidity, our results do not support this confirmation made by previous studies in SSA (33,36,38). Thus, in the conclusions of some studies, multimorbidity was significantly more observed in physically inactive or sedentary people (82). The increased risk could be explained by the fact that either people lead more sedentary lives or conversely the occurrence of multimorbidity limits and considerably reduces the physical activities of the person. The physical abilities of the elderly are constantly decreasing to the point that the ability to physiological adaptation remains a problem. However, muscle strengthening through physiotherapy exercises would reduce the risk of inactivity and therefore reduce the risk of frailty and multimorbidity. Consequently, the establishment of a national policy focused on the establishment of a balanced diet and the practice of sports activities from the age of 50 is an innovative approach to reduce the incidence of frailty and multimorbidity. In addition, community initiatives must be deployed for the development of the place of residence or the implementation of rehabilitation programs and community physical activities.

### 5.1.3. Medical-clinical determinants of frailty and multimorbidity

The risk of developing frailty in the group of underweight participants was 26 times the risk of frailty in the other groups. This finding supports the hypothesis of a causal association between frailty and underweight-defined malnutrition (77). In previous studies, the risk of onset of frailty was strongly correlated with underweight characterized by malnutrition (57,77). However, these underweight participants had a 60% reduction in risk of developing multimorbidity compared to other participants. This demonstration is in discrepancy with certain conclusions where underweight has been identified as a major determinant of increased risk of multimorbidity (33,38,84). The discrepancy in conclusions could be related to the method of assessing the concept

of malnutrition. The concept of malnutrition is characterized by an imbalance between protein-energy needs and nutritional intake leading to changes in body functions and body composition. These changes lead to a micronutrient deficit. In previous studies, the risk of frailty and multimorbidity was weakly associated with a high-calorie diet (78). Similarly, vitamin D deficiency and deficits in total protein-calorie intake increased the risk of developing frailty or multimorbidity (78,79). However, a healthy diet significantly reduced the risk of these conditions. Overweight participants were 5.0 more likely to have multimorbidity while obesity increased the risk of developing multimorbidity by 240%. Our results support the findings of previous studies on the increased effect of overweight and obesity in the development of multimorbidity (33,59,60). Similarly, our analyses are consistent with the conclusions of studies conducted in SSA where the increase in BMI significantly increased the risk of multimorbidity (18,82). In addition, overweight and obesity have been reported as contributing factors to multimorbidity in SSA (59,82). Overweight and obesity are major determinants that characterize the direct consequence of unhealthy eating behavioural attitudes and a sedentary lifestyle. The presence of these conditions symbolizes an excessive or abnormal accumulation of body fat which increases the risk of developing cardiovascular diseases, diabetes, hypertension (11). Community initiatives for vitamin supplements and food should be developed for underweight elderly people to reduce nutritional deficits. Vitamin D supplementation helps build bone density and improve muscle strength. In addition, a healthy diet and regular exercise offer the possibility of reducing or preventing overweight, obesity and the various associated risk factors.

Weight loss and self-reported exhaustion were the most frequently observed phenotypic components in almost a quarter of participants. Similar observations have been reported in previous studies (21,26,43). Almost two-thirds of participants were pre-frail (59.3%) while less than one-tenth of participants were frail (8.5%). The present prevalence of frailty is similar to that described (7%) by Miles et al., in 2015 in rural Burkina Faso (26). Likewise, this prevalence is consistent with that described by Collin et al., in South Africa, where it varied between 3.5 and 13.4% (21). However, the prevalence of pre-frailty is higher compared to previous studies conducted in SSA where it varied between 20 and 40% (21,26,43). The different frailty assessment measures would partially explain the observed variations in prevalence. Similarly, the heterogeneity of the group of elderly people with genetic medical history, different biological environmental factors would

explain the variations in the prevalence of frailty. As for multimorbidity, it prevailed in more than a third of the population (38.3%) with an incidence of 13 per 100 participants. This prevalence is clearly increasing compared to that of a previous study conducted in rural Burkina Faso (18,27). The main reason for this increase could be related to the increase in the proportions of chronic conditions, the increase in the age of the participant and other major determinants. However, this prevalence is lower than that of a study conducted in an urban environment (28). The difference is explained by the rural area and the inclusion age of the participants, which was over 65 years old in the study by Hien et al in 2015 (28). In addition, dyslipidaemia and hypertension and rheumatic arthritis were the more reported consistent with the findings of previous studies (18,27,28). The main reason for an increase in chronic diseases is probably due to the development of certain chronic diseases which constitute predisposing factors for other chronic diseases (77).

We reported that nearly half of participants who had multimorbidity were frail (47.2%), while one-tenth of frail participants had multimorbidity (10.4%). This suggests that there are likely additional pathways for the occurrence of frailty and multimorbidity (9,69). Thus, frailty and multimorbidity are far from being synonymous expressions whose bidirectional relationship remains poorly understood. This problem is linked to the facts, that they are relatively recent and that there is a disparity in definitions and evaluation methods (4,6–8). Additionally having multimorbidity was 1.4 times more likely to be frail than pre-frail and robust while the risk of multimorbidity was 1.8 and 2.1 times higher for pre-frail and frail participants, respectively. These findings support the hypothesis of the bidirectional causal association between frailty and multimorbidity and are consistent with those of previous studies (27,34,42). In many previous studies, the occurrence of frailty is influenced by the presence of chronic diseases (9,34,77). In contrast, the increased risk of multimorbidity is influenced by increased risk of frailty (27,77). The functional repercussions of the diseases and the possibility of iatrogenic effects of the various treatments probably explain the increased risk (9,40,77). Similarly, one of the main reasons why individuals become frail is related primarily to the physiological changes of aging exemplified by sarcopenia (9,69). Therefore, the establishment of outpatient monitoring in geriatric units will reduce the risk of vulnerability. Similarly, strengthening early detection followed by medication reconciliation at appropriate times will offer the possibility of risk reduction. Epidemiological surveillance of chronic disease trends

and associated modifiable risk factors is one of the low-cost initiatives aimed at reorienting priorities and targeted adhesive policies.

## 5.2. Clinical relevance of the findings

This study makes an important contribution to improving knowledge of frailty and multimorbidity as different physiological geriatric syndromes. Similarly, this study removes the ambiguity between frailty and multimorbidity wrongly treated as synonymous terms. Moreover, our findings provide further demonstration on the sociodemographic determinants, lifestyle determinants, and clinical determinants of frailty and multimorbidity in SSA. The hypothesis on the bidirectional association between frailty and multimorbidity is supported through the findings of this study in rural low-resource settings such as Burkina Faso. Moreover, the determination of the frailty score constitutes an approach in clinical practice to identify vulnerable people with an increased susceptibility to frailty. In addition, highlighting risk factors for frailty and multimorbidity will guide strategic efforts in appropriate programs to potentially reduce modifiable risk factors. Similarly, the demonstration of the findings of this study constitutes a necessary database that can be used to develop care strategies and interventions adapted to the elderly.

## 5.3. Strengths and limitations of the study

This study is one of the rare longitudinal studies on frailty and multimorbidity in SSA and more particularly in Burkina Faso. Moreover, the strength of this study is related to the relatively large sample size including middle-aged adults, implying a better representativeness of this population that can accurately provide conclusive results. The collection of detailed sociodemographic, lifestyle and clinical information is a main strength that can help identify the determinants of frailty and multimorbidity. In addition, the evaluation of multimorbidity in the baseline study constitutes a strength to the point that it made it possible to evaluate the cumulative incidence of multimorbidity and the rate of multimorbidity stratified by the number of existing chronic diseases at the follow-up study. Similarly, the need to conduct prospective studies was highlighted through this study with the aim of determining the incidence and predictors of frailty in urban settings.

The main limitation of this study was the absence of the evaluation of the components of frailty as dependent variables at the baseline study, so that the analysis of this dependent variable at the follow-up study lends itself to a cross-sectional conception limiting any conclusion on the causality.

Thus, the assessment of frailty through a cross-sectional design could lead to an under- and/or over-estimation of the different components of frailty. In addition, the longitudinal nature of the study constitutes a limitation based on the follow-up of the participants. There was a loss of a large proportion of the number of participants who could not be included in the follow-up visit for reasons of deliberate refusal and possible exclusion for participants who left their usual place of residence without having communicated this to the research centre. This constitutes a source of information bias influencing the evaluation of the main outcomes. Recall bias may be observed because information from the orally administered questionnaire may have been truncated or reported with forgetting errors. Similarly, the fact that the majority of participants were illiterate constitutes a recall bias in the sense that these participants would have had difficulty in accurately translating the chronic diseases diagnosed by health professionals. This may therefore lead to an underestimation of the prevalence of these chronic diseases. In addition, a limit could be notified related to the behavioural changes of the participants during the past five years. Furthermore, the fact that the majority of the population comes from rural areas is a limitation in the sense that the participants share experiences differently. The rural site of the study limits a broad assessment of frailty and multimorbidity, because the urban setting seems to be the area susceptible to multimorbidity according to several studies. Thus, the generalization of the findings of this study to the entire population remains limited, as does the understanding of similarities and differences at epidemiological stages of transition. Finally, this study does not make it possible to assess frailty and multimorbidity in participants outside the age of 40-65 years old.

## 5.4. Conclusion

In conclusion, we determined factors associated with frailty and multimorbidity in 1500 middle-aged adults aged 40-65 years followed from 2015 to 2022 in Burkina Faso. Our findings show a prevalence of almost two-thirds and one-tenth of pre-frailty and frailty respectively. Likewise, more than a third of the study population had a multimorbidity. On the one hand, increasing age (≥ 50 years), having a deceased partner, being unemployed, smokeless tobacco use, being underweight, and multimorbidity were independently associated with increased risk of frailty. However, increased consumption of fruit and vegetables servings, and being highly active in weekly activities significantly reduced the risk of frailty. On the other hand, increasing age (≥ 60 years), being a woman, having a deceased partner, being unemployed, being overweight, being

obese, pre-frailty and frailty were independently associated with an increased relative risk ratio of multimorbidity. Nevertheless, the consumption of alcohol and the consumption of fruit servings significantly reduced the risk of multimorbidity. The findings of this study thus provide additional evidence on the risk factors and on the hypothesis of the bidirectional association between frailty and multimorbidity in low-resource rural settings. The optimization of the management of frailty, and multimorbidity must be done through a multisectoral approach of screening, treatment and prevention from the age of 50, in women, people in a situation of obesity and people of low socioeconomic status. Community awareness initiatives should be strengthened to influence lifestyle of the participants on tobacco consumption, alcoholism, physical activity, and vitamin supplementation associated with increased consumption of fruit and vegetable servings.

## 5.5. Recommendations

In the context of determining the factors associated with frailty and multimorbidity in middle-aged adults, the findings suggest that, given the growing number of chronic diseases, the establishment of an epidemiological surveillance plan is necessary to control and limit the risk of vulnerabilities and chronic diseases among exposed people. The surveillance plan is a primary epidemiological method for understanding the distribution of a disease at the population level. This plan will be used to guide efforts to control risk factors and limit the incidence of chronic diseases leading to frailty and multimorbidity. In particular, this will be to:

**To the Ministry of Health and Public Hygiene:**

- Establish a national plan for epidemiological surveillance of the progression of chronic disease trends as well as the associated modifiable risk factors to reorient the priorities and the policies targeted towards the achievement of the Sustainable Development Goals.
- Establish a national plan oriented on the establishment of a balanced diet and the practice of sports activities from the age of 50 in order to reduce the incidence of frailty and multimorbidity.
- Optimize the management of frailty and multimorbidity through multisectoral collaboration among vulnerable people, particularly people over 50, widowed women, people of low socio-economic status while redirecting the allocation of resources to this group.
- Integrate geriatric medicine services in health facilities to facilitate the assessment and understanding of the heterogeneity of health states in the elderly.

**To the National Institute of Public Health:**

- Recognize frailty and multimorbidity as disabling conditions and consider early intervention measures to reverse and delay certain evolutionary aspects.
- Initiate comprehensive geriatric assessments (CGA) at individual and community level, physical activity and social engagement to help the elderly.
- Deploy community initiatives for the development of the place of residence or the implementation of community rehabilitation and physical activity programs.
- Develop community initiatives to strengthen vitamin supplementation associated with increased daily consumption of at least 5 servings of fruits and vegetables as recommended by WHO.

**To the Health Sciences Research Institute:**

- Conduct in-depth prospective stratification studies by area to assess the incidence and determinants of frailty and multimorbidity in order to establish potential interventions to reduce increased risk.
- Carry out the additional investigations necessary to establish the direction of the causal relationship of certain determinants and for a targeted reorientation of prevention strategies.

**To the Chief Medical Officers of the Health Districts:**

- Establish outpatient monitoring of the elderly in geriatric departments while working on early detection followed by medication reconciliation and food supplementation at appropriate times to control risks.
- Systematically identify people aged over 50 to establish prospects for screening, detection, treatment and risk prevention.

**To Healthcare professionals:**

- Deploy awareness initiatives to promote healthy eating and to influence the lifestyle of the population on tobacco consumption, alcoholism and physical activity.

**To the whole population, especially middle-aged adults:**

- Adopt a healthy diet coupled with regular physical exercise to reduce or prevent overweight, obesity and the various associated risk factors.

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# APPENDICES

## Appendix 1: Plagiarism declaration report




**PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS**

SENATE PLAGIARISM POLICY: APPENDIX ONE

I _____**Georges Some**_____ (Student number: ____**2603815**_____) am a student registered for the degree of __**Epidemiology and Biostatistics**__ in the academic year _**2023**_.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: ___**10 JANUARY 2024**_____

## Appendix 2: Ethics clearance certificate

M230232 MED23-01-069

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Georges Some

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**

**CLEARANCE CERTIFICATE NO. M230232 MED23-01-069**

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr Georges Some |
| **DEPARTMENT:** | Epidemiology and Biostatistics<br>Health District of Nanoro and Yako in BURKINA FASO |
| **PROJECT TITLE:** | Predictors of frailty and multimorbidity in adults aged 40 to 65 in a rural population cohort in Burkina Faso |
| **DATE CONSIDERED:** | 24/02/2023 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Prof N. Kandala, Dr J. Kagura and Dr P. Boua |
| **APPROVED BY:** | Dr C Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 03/04/2023 **EXPIRY DATE:** 03/04/2028 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

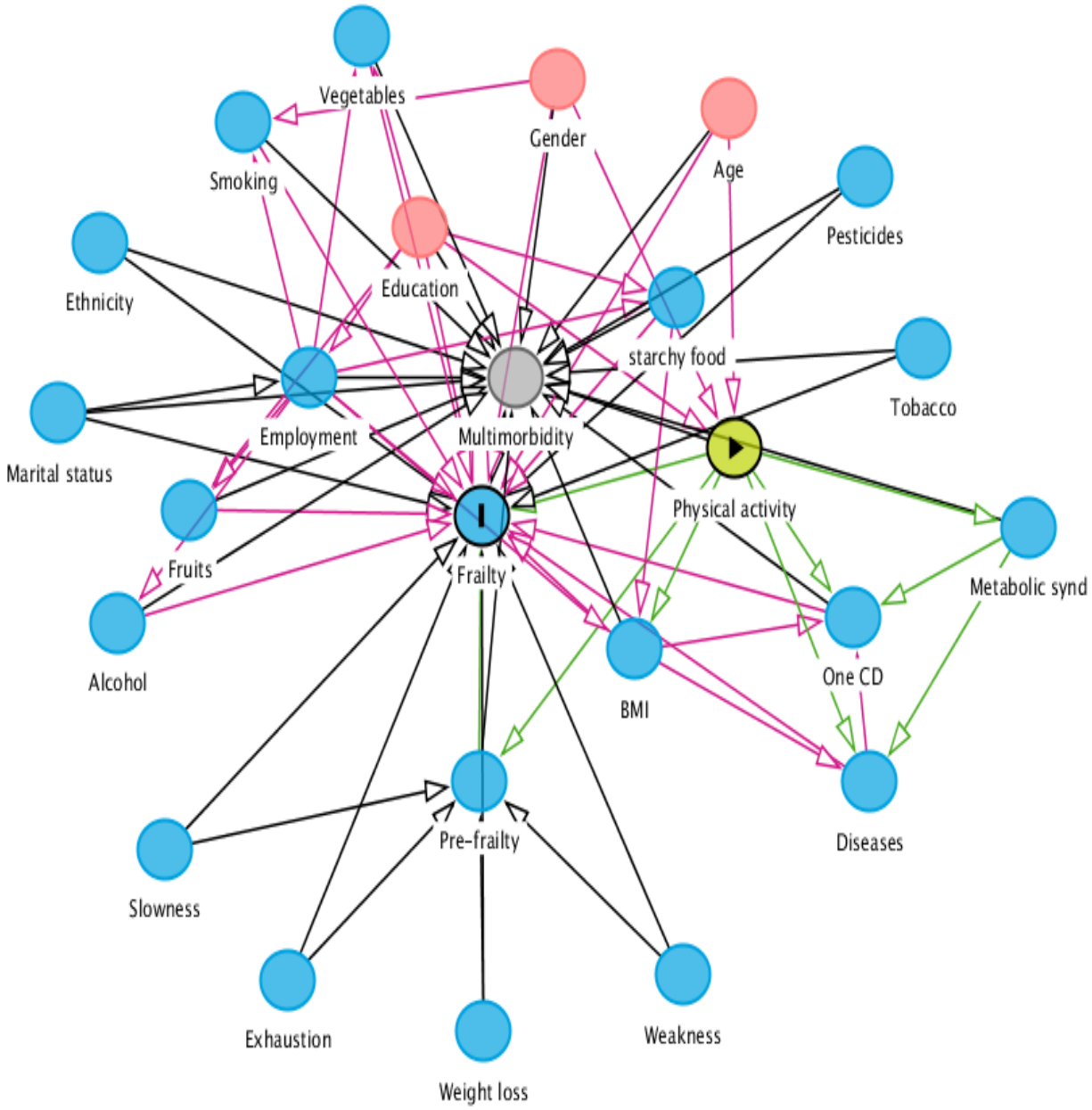
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in January each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Login to upload signed copy of this ethics clearance certificate prior to commencing with the study https://www.witsethics.co.za/login.aspx

Principal Investigator Signature

12 April 2023
Date

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

## Appendix 3: Directed acyclic graphs of interrelationships between variables



## Appendix 4: Multiple imputation multivariate normal distribution sensitivity analysis

**Baseline study data**

```
Performing MCMC data augmentation ...
Multivariate imputation                       Imputations =        5
Multivariate normal regression                      added =        5
Imputed: m=1 through m=5                          updated =        0

Prior: uniform                                 Iterations =      500
                                                  burn-in =      100
                                                  between =      100
```

| | Observations per m | | | |
|---|---|---|---|---|
| Variable | Complete | Incomplete | Imputed | Total |
| age1 | 1498 | 2 | 2 | 1500 |
| agegroup1 | 1498 | 2 | 2 | 1500 |
| sex1 | 1498 | 2 | 2 | 1500 |
| ethnic1 | 1497 | 3 | 3 | 1500 |
| marital1 | 1496 | 4 | 4 | 1500 |
| educ1 | 1490 | 10 | 10 | 1500 |
| employ1 | 1495 | 5 | 5 | 1500 |
| smoke1 | 1496 | 4 | 4 | 1500 |
| smokeless1 | 1481 | 19 | 19 | 1500 |
| alcohol1 | 1493 | 7 | 7 | 1500 |
| prob_drink1 | 1498 | 2 | 2 | 1500 |
| fruit1 | 374 | 1126 | 1126 | 1500 |
| vegetables1 | 1150 | 350 | 350 | 1500 |
| bread1 | 542 | 958 | 958 | 1500 |
| mvpa_c | 1498 | 2 | 2 | 1500 |
| mvpa_cat_c | 1497 | 3 | 3 | 1500 |
| pesti1 | 1495 | 5 | 5 | 1500 |
| bmi_qc | 1498 | 2 | 2 | 1500 |
| Cat_BMI1 | 1498 | 2 | 2 | 1500 |
| MetS1 | 1498 | 2 | 2 | 1500 |
| SBP1 | 1498 | 2 | 2 | 1500 |
| morbtot1 | 1498 | 2 | 2 | 1500 |
| asthma1 | 1382 | 118 | 118 | 1500 |
| diabetes1 | 1498 | 2 | 2 | 1500 |
| CVD1 | 1484 | 16 | 16 | 1500 |
| hypertension1 | 1461 | 39 | 39 | 1500 |
| thyroid1 | 1494 | 6 | 6 | 1500 |
| CKDis1 | 1494 | 6 | 6 | 1500 |

```
(Complete + Incomplete = Total; Imputed is the minimum across m
 of the number of filled-in observations.)
```

**Follow-up study missing data**

```
Performing EM optimization:
  observed log likelihood = 19491.843 at iteration 6

Performing MCMC data augmentation ...

Multivariate imputation                       Imputations =       10
Multivariate normal regression                      added =        5
Imputed: m=6 through m=10                         updated =        0

Prior: uniform                                 Iterations =      500
                                                  burn-in =      100
                                                  between =      100
```

| | Observations per m | | | |
|---|---|---|---|---|
| Variable | Complete | Incomplete | Imputed | Total |
| ethnic | 1498 | 2 | 2 | 1500 |
| marital | 1491 | 9 | 9 | 1500 |
| educ | 1493 | 7 | 7 | 1500 |
| employ2 | 1494 | 6 | 6 | 1500 |
| smoke | 1494 | 6 | 6 | 1500 |
| smokeless | 1494 | 6 | 6 | 1500 |
| alcohol | 1494 | 6 | 6 | 1500 |
| fruit | 1493 | 7 | 7 | 1500 |
| vegetables | 1493 | 7 | 7 | 1500 |
| bread | 1488 | 12 | 12 | 1500 |
| pesti | 1492 | 8 | 8 | 1500 |
| cancer | 1471 | 29 | 29 | 1500 |
| current_tb | 1496 | 4 | 4 | 1500 |
| asthma | 1493 | 7 | 7 | 1500 |
| retinal | 1440 | 60 | 60 | 1500 |
| CVD | 1484 | 16 | 16 | 1500 |
| hypertension | 1494 | 6 | 6 | 1500 |
| thyroid | 1491 | 9 | 9 | 1500 |
| CKDis | 1486 | 14 | 14 | 1500 |
| arthritis | 1493 | 7 | 7 | 1500 |
| dyslipidemia | 1498 | 2 | 2 | 1500 |

```
(Complete + Incomplete = Total; Imputed is the minimum across m
 of the number of filled-in observations.)
```

## Appendix 5: Turnitin report



## Appendix 6: List of extracted and recoded variables

| | | |
|---|---|---|
| | **AWI-Gen Study Number:** | |
| | **Unique site identifier** | **TA…..** |
| **1. GENERAL INFORMATION** | | |
| **1.1** | **Date of Collection** | |
| **1.2** | **Interviewer code** | |
| **1.3** | **Start time** | |
| **2. DEMOGRAPHIC INFORMATION** | | |
| **2.2** | **Date of Birth** | |
| **2.3** | **Year of birth** | |
| **2.4** | **Gender** | |
| **2.5** | **Country** | |
| **2.7** | **Ethnic/tribal affiliation** | |
| **5.1** | **5.1 MARITAL STATUS** | |
| **5.1.1** | **Marital Status** | |
| **5.2** | **5.2 EDUCATION** | |
| **5.2.1** | **Highest level of Education.** | |
| **5.2.2** | **Total number of successfully completed years at highest level of education.** | |
| **5.2.3** | **What is the total number of years you have received in education formal.** | |
| **5.3** | **5.3 EMPLOYMENT (Main occupation)** | |
| **5.3.1** | **Main occupation during the 12 last months.** | |
| **5.3.2** | **How many day(s) do you work in the week?** | |
| **6.b. Measurement of physical weakness (frailty component)** | | |
| **6.4** | **6.4. Assessment of the standing-sitting position** | |
| **6.4.1** | **We will ask you to get up and sit down five times as fast as possible. (Note in seconds with one decimal).** | |
| **6.4.2** | **Did the participant use their hands during the procedure?** | |
| **6.4.3** | **Did the participant stand up and sit down five times?** | |
| **6.4.3** | **If not, say why** | |
| **6.5** | **6.5. grip strength** | |
| **6.5.1** | **What is your dominant hand? (Perform the test with the non-dominant hand).** | |
| **6.5.2** | **How hard did the participant squeeze the dynamometer the first time?** | |
| **6.5.3** | **How hard did the participant squeeze the dynamometer the second time?** | |
| **6.5.4** | **How hard did the participant squeeze the dynamometer the third time?** | |
| **6.5.5** | **Did the participant complete the session?** | |
| **6.5.6** | **If not, say why.** | |
| **6.6** | **6.6. Five meters walk** | |
| **6.6.1** | **We are going to ask you to walk as fast as you can until at the line (2.5 m), turn around and come back. (Note in seconds with one decimal)** | |
| **6.6.2** | **Did the participant require any physical assistance during theprocedure?** | |
| **6.6.3** | **Did the participant complete the session?** | |

| | | |
|---|---|---|
| **6.6.4** | **If not, say why** | |
| **8. SUBSTANCE USE** | | |
| **8.1** | **8.1. Tobacco use** | |
| **8.1.1** | **Have you ever smoked any tobacco products such as cigarettes, cigars or pipes?** ***[If no, skip to Q.9.1.8]*** | |
| **8.1.2** | **Have you smoked more than 100 times in your life** | |
| **8.1.3** | **Do you *currently smoke any tobacco products, such as cigarettes, cigars or pipes?** ****We are asking if they smoke when they have the opportunity to do so. [If no, skip to Q.9.1.6] [If yes, please do not answer Q.9.1.7]*** | |
| **8.1.4** | **Have you smoked in the past hour?** | |
| **8.1.5** | **What do you smoke?** | |
| **8.1.6** | **How often do you smoke tobacco products?** | |
| **8.1.7** | **On the days you smoke, how many tobacco products do you smoke per day?** | |
| **8.1.8** | **How old were you when you started to smoke?** | |
| **8.1.9** | **When did you stop smoking completely?** | |
| **8.1.10** | **Have you ever used other tobacco products, such as snuff, betel with tobacco or chewing tobacco? [ if NO, go to Q 8.2]** | |
| **8.1.11** | **Do you use snuff? [ if NO, go to Q89.1.13]** | |
| **8.1.12** | **How do you take snuff?** | |
| **8.1.13** | **How often do you use snuff?** | |
| **8.1.14** | **On the days you use snuff, how many times per day do you use it?** | |
| **8.1.15** | **Do you use chewing tobacco? [ if NO, go to Q.8.2]** | |
| **8.1.16** | **How often do you use chewing tobacco?** | |
| **8.1.17** | **On the days that you use chewing tobacco, how many times a day do you use it?** | |
| **8.2** | **8.2. Alcohol consumption** | |
| **8.2.1** | **Have you ever consumed an alcoholic drink such as beer, wine, spirits, fermented cider, or traditional beer?** ***[If"no" or "don't know", skip to Q.8.3]*** | |
| **8.2.3** | **Do you currently (in the last 30 days) consume any alcoholic drink such as beer, wine, spirits, fermented cider, or traditional beer?** ***[If no, skip to Q.8.2.10]*** | |
| **8.2.4** | **How often do you have at least one alcoholic drink?** | |
| **8.2.4** | **On the days that you drink alcoholic drinks, how many alcoholic drinks do you have? Use cards to show standard drinks.** | |
| **8.2.5** | **Have you ever felt that you should cut down on your drinking?** | |
| **8.2.6** | **Have people annoyed you by criticizing your drinking?** | |
| **8.2.7** | **Have you ever felt bad or guilty about your drinking?** | |
| **8.2.8** | **Have you ever had an alcoholic drink first thing in the morning to steady your nerves or get rid of a hangover?** | |
| **8.2.9** | **In the past year, did you ever take 6 or more alcoholic drinks in a single morning, afternoon, or night? I understand that you may share drinks and that some drinks have different sizes, but please do your best to answer. Use cards to show standard drinks.** | |
| **8.2.10** | **What type of alcoholic beverage do you, or did you, usually drink?** | |
| **8.3** | **8.3. Drug use** | |

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| **8.3.1** | **Have you ever used marijuana?** | |
| **8.3.2** | **Have you ever used methamphetamines, cocaine or any other drugs whatsoever?** | |
| | **GENERAL HEALTH** | |
| **9.a** | **9.a GENERAL HEALTH-Cancer** | |
| **9.1.1** | **Breast cancer *[for females only]*** | |
| **9.1.2** | **Cervical cancer *[for females only]*** | |
| **9.1.3** | **Prostate cancer *[for males only]*** | |
| **9.1.4** | **Esophageal cancer** | |
| | **Asthma or reactive air diseases** | |
| **9.1.5** | **Other cancers** | |
| **9.1.5.1** | **To specify** | |
| **9.c** | **9.c. GENERAL STATE OF HEALTH-Dietary**<br>**The following questions are about what you eat and drink** | |
| **9.4.2** | **How many servings of fruit do you eat on a typical day?**<br>***Use cards to show standard servings*** | |
| **9.4.4** | **How many servings of vegetables do you eat on a typical day?** | |
| **9.4.5** | **What is the main source of carbohydrates in your diet?** | |
| **9.4.6** | **In a week, how often can you eat carbohydrate-rich foods?** | |
| **9.4.7** | **How many servings of carbohydrate-rich foods do you eat each day? where do you eat it?** | |
| **9.4.9** | **How many cans, bottles, or cups of sugary cold drinks (eg. Coke, Fanta, Sprite, malta, tonic, etc.), do you drink in a week?** | |
| **9.4.10** | **How many cans or bottles or cups of fruit juice do you drink in a week? (eg. Dafani, Frutelli, Tampico, Ivory, etc.)** | |
| **9.d** | **9.d. GENERAL HEALTH - Exposure to pesticides** | |
| **9.5.1** | **Do you work with insecticides or pesticides?** | |
| **9.5.2** | **How long have you been working with insecticides or pesticides?** | |
| **9.5.3** | **Do you live close to a farm or region where insecticides or pesticides are used?** | |
| **9.6** | **9.d. GENERAL HEALTH - Exposure to pesticides** | |
| **9.6.6** | **Do you use insecticides in the house (mostico, sprayers)?** | |
| **10** | **INFECTION HISTORY** | |
| **10.1** | **Malaria** | |
| **10.1.1** | **Have you ever had Malaria?** | |
| **10.1.2** | **Have you had malaria fever in the last month?** | |
| **10.2** | **Tuberculosis** | |
| **10.2.1** | **Have you ever been told by a doctor, nurse or other healthcare worker that you have TB?** | |
| **10.2.2** | **Have you been newly-diagnosed with TB in the last 12 months?** | |
| **10.2.3** | **When was it diagnosed?** | |
| **10.3** | **VIH** | |
| **11** | **CARDIOMETABOLIC RISK FACTORS** | |
| **11.a** | **11.a CARDIOMETABOLIC RISK FACTORS-Diabetes** | |

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| **11.1.1** | **Have you ever been told by a doctor or healthcare worker, that you have diabetes or high blood sugar (outside of pregnancy)?** | |
| **11.1.2** | **Have you been newly-diagnosed with diabetes in the last 12months?** | |
| **11.1.9** | **Do you have a family history of diabetes?** | |
| **11.b** | **11.b CARDIOMETABOLIC RISK FACTORS-Heart conditions** | |
| **11.2** | **11.2. Stroke*** | |
| **11.2.1** | **Have you ever been told by a doctor, nurse, or other healthcare worker that you have had a stroke?** | |
| **11.2.2** | **When was it first diagnosed?** | |
| **11.2.3** | **Have you ever been told by a doctor, nurse, or other healthcare worker that you have had a ministroke, or transient ischemic attack (TIA)?** | |
| **11.2.4** | **Have you ever had sudden painless weakness on one side of your body?** | |
| **11.2.5** | **Have you ever had sudden numbness or a dead feeling on one side of your body?** | |
| **11.2.6** | **Have you ever had sudden painless loss of vision in one or both eyes?** | |
| **11.2.7** | **Have you ever suddenly lost one half of your vision?** | |
| **11.2.8** | **Have you ever suddenly lost the ability to understand what people are saying?** | |
| **11.2.9** | **Have you ever suddenly lost the ability to express yourself verbally, or in writing?** | |
| **11.3.** | **11.3. Angina pectoris*** | |
| **11.3.1** | **Have you ever been told by a doctor, nurse, or other healthcare worker that you have angina (chest pain due to heart disease)?** | |
| **11.4** | **11.4. Heart Attack** | |
| **11.4.1** | **Have you ever been told by a doctor, nurse, or other healthcare worker that you have had a heart attack?** | |
| **11.5.** | **11.5. Congestive Heart Failure** | |
| **11.5.1** | **Have you ever been told by a doctor, nurse, or other healthcare worker that you have had heart failure?** | |
| **11.6.** | **11.6. Hypertension** | |
| **11.6.1** | **Has a doctor, nurse, or other healthcare worker ever measured your blood pressure?** | |
| **11.6.2** | **Have you ever been told by a doctor, nurse, or other healthcare worker that you have hypertension (high blood pressure)?** | |
| **11.6.3** | **Have you been newly-diagnosed with hypertension in the last 12 months?** | |
| **11.7.** | **11.7. High Cholesterol** | |
| **11.7.** | **Has a doctor, nurse or other healthcare worker ever measured your cholesterol?** | |
| **11.7.4** | **Are you currently using any of the following to treat your high cholesterol, as prescribed by a doctor, nurse, or other healthcare worker?** | |
| **11.8** | **11.8. THYROID DISEASE*** | |
| **11.8.1.** | **Has a doctor ever told you that you have thyroid disease?** | |
| **11.8.2** | **Do you know what type of thyroid disease you were diagnosed with? If yes, please specify** | |
| **11.9.** | **KIDNEY DISEASE** | |
| **11.9.1** | **Has a doctor ever told you that you have kidney disease?** | |

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| **11.9.2** | **Do you know what type of kidney disease? If yes please specify.** | |
| **11.9.3** | **Has a doctor ever told you that your kidneys have low function?** | |
| **11.9.6** | **Do you know what kind of kidney disease he or she had? If yes, please specify.** | |
| **11.10** | **11.10 Rheumatic Arthritis** | |
| **11.10.1** | **Have you ever had swollen or painful joints?** | |
| **11.10.2** | **How many joints are swollen or painful?** | |
| **11.10.6** | **Have you ever been tested and received your exam results? following laboratories to diagnose rheumatism?** | |
| **11.10.7** | **Rheumatoid factor** | |
| **11.10.8** | **Protein Anti-citriline antibody** | |
| **11.10.9** | **ESR and/or CRP** | |
| **12.** | **12. PHYSICAL ACTIVITY** | |
| **12.1.1** | **How many days do you work per week?** | |
| **12.2** | **Occupation-related Physical Activity (paid or unpaid work)** | |
| **12.2.2** | **Does your work involve vigorous activities (heavy lifting, digging, manual labour or construction) for at least 10 minutes at a time?** | |
| **12.2.3** | **In a usual week, how many days are spent doing vigorous activities as part of your work?** | |
| **12.2.4** | **On a usual day of vigorous work, how many hours are spent doing these activities?** | |
| **12.2.5** | **Does your work involve moderate-intensity activities (brisk walking or carrying light loads) for at least 10 minutes at a time?** | |
| **12.2.6** | **In a usual week, how many days are spent doing moderate intensity activities at work?** | |
| **12.2.7** | **On a usual work day, how many hours are spent doing moderate-intensity activities?** | |
| **12.2.8** | **How long is your usual work day? *[Please indicate how many hours you work per day on average]*** | |
| **12.3.** | **12.3. Travel-related physical activity** | |
| **12.3.1** | **Do you walk or use a bicycle (for at least 10 minutes at a time) to get to and from places?** | |
| **12.3.2** | **In a usual week, how many days do you walk or cycle for at least 10 minutes to get to and from places?** | |
| **12.4** | **12.4 Non-work related and leisure time Physical Activity** | |
| **12.4.1** | **In your spare time, do you engage in any vigorous or moderate intensity physical activities lasting more than 10 minutes at a time?** | |
| **12.4.2** | **In your spare time do you do any vigorous activities like running, strenuous sport or exercise for at least 10 minutes at a time?** | |
| **12.4.3** | **In a usual week, how many days do you engage in vigorous activities as part of your leisure time?** | |
| **12.4.4** | **In a normal day, how many leisure hours are spent doing vigorous activities?** | |

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| **12.4.5** | **In your spare time, do you engage in any moderately intense physical activities like walking or swimming for at least 10 minutes at a time?** | |
| **12.4.6** | **In a normal week, how many days are spent engaging in moderately intense physical activity as part of your leisure time?** | |
| **12.4.7** | **How many leisure hours are spent doing moderate-intensity activities in a normal day?** | |
| **12.5** | **Sitting/Resting Activity** | |
| **12.5.1** | **During a working day, how many hours did you spend sitting or reclining on a usual day (excluding sleep)? This may include time sitting at a desk, visiting friends, reading, or sitting down to watch television during working hours and leisure or spare time. During the last 7 days, how many hours did you spend sitting** | |
| **12.5.2** | **During a rest day, how many hours did you spend sitting or reclining on a usual day (excluding sleep)? This may include time sitting at a desk, visiting friends, reading, or sitting down to watch television during working hours and leisure or spare time. During the last 7 days, how many hours did you spend sitting** | |
| **12.6** | **SLEEP** | |
| **12.6.1** | **What time do you go to sleep during the week?** | |
| **12.6.2** | **What time do you wake up during the week?** | |
| **12.6.3** | **What time do you go to sleep during the weekend?** | |
| **12.6.4** | **What time do you wake up during the weekend?** | |
| **12.6.9** | **What time of day do you feel most alert? fit and energetic?** | |
| **12.6.13** | **Do you ever wake up and feel tired?** | |
| | **SAMPLE COLLECTION DATA** | |
| **13.** | **13. ANTHROPOMETRIC MEASUREMENTS** | |
| **13.1** | **Standing height** | |
| **13.2** | **Weight** | |
| **13.3** | **Waist circumference** | |
| **13.4** | **Hip circumference** | |
| **14** | **14. BLOOD PRESSURE** | |
| **15.** | **15. ULTRASOUND MEASUREMENTS** | |
| **15.1.** | **15.1 Visceral and abdominal fat measurements** | |
| **15.1.1** | **Visceral (medial) fat** | |
| **15.1.2** | **Subcutaneous (transverse) fat** | |
| **15.2** | **15.2 Carotid intima-media thickness** | |
| **15.2.5** | **Mean cIMT on the right** | |
| **15.2.6** | **Mean cIMT on the left** | |
| **15.3** | **15.3 Search for atheroma plaque** | |
| **15.3.1** | **Plate measured** | |
| **16.a** | **16.a Respiratory health** | |
| **16.1.** | **16.1 Questions related to lung function** | |
| **16.1.2** | **Has a doctor ever told you that you have asthma?** | |

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| **16.1.3** | **Has a doctor or other healthcare professional ever told you that you had one of the following conditions?** | |
| **16.1.5** | **Have you ever suffered from any of the following illnesses?** | |
| **16.2.** | **16.2 Questions related to lung function** | |
| **18** | **18. Test Results** | |
| | **Fasting Plasma Glucose** | |
| | **Fasting Insulin** | |
| | **HbA1c** | |
| | **HDL** | |
| | **LDL** | |
| | **Triglycerides** | |
| | **Total Cholesterol** | |