筑　波　大　学

博士（医学）学位論文

Relationship of muscle strength, body composition and incident prediabetes among adults

(成人における筋力、体組成の前糖尿病発生との関係)

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Abbreviations and acronyms

T2DM	Type 2 diabetes mellitus
NCD	Non-communicable disease
BMI	Body mass index
COI	Center of Innovation program of Japan
JA Ibaraki	Japan Agriculture Cooperative of Ibaraki
MEIRU	Malawi Epidemiology and Intervention Research Unit
HR	Hazard ratio
aHR	Adjusted hazard ratio
OR	Odds ratio
aOR	Adjusted odds ratio
CI	Confidence interval
SE	Standard error
SSA	Sub-Saharan Africa
GLUT-4	Glucose transporter type 4
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
HbA1c	Haemoglobin A1c
FPG	Fasting plasma glucose
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
SD	Standard deviation

ANOVA	Analysis of variance
VIF	Variance inflation factors
SPSS	Statistical Package for the Social Sciences
FFM	Fat-free mass
OGTT	Oral glucose tolerance test
DOHaD	Developmental Origins of Health and Disease hypothesis
NHSRC	National Health Sciences Research Committee
HDSS	Health, and Demographic Surveillance Site
WHO	World Health Organization
STEPS	STEPwise approach to Surveillance
BIA	Bioelectrical impedance analysis

Summary

Introduction: Global prevalence of prediabetes and type 2 diabetes mellitus (T2DM) is rising rapidly. Early intervention in prediabetic individuals significantly reduces the risk of progression to T2DM. Thus, identifying individuals at higher risk of prediabetes would provide the best opportunity to implement preventive strategies. Shared risk factors for non-communicable diseases (NCDs), such as obesity, are well reported. However, contrary to data from western populations, studies from Sub-Saharan Africa (SAA) and Asia show that a substantial proportion of people with diabetes are not overweight or obese. One possible explanation might relate to the limitation of body mass index (BMI) since it lacks sensitivity for assessing disease risks, especially in people with normal or mildly elevated body weight. Low muscle strength has recently been suggested as another modifiable risk factor for T2DM. However, some studies do not report such an association, while others suggest reverse causation. Furthermore, no studies investigated the relationship between muscle strength and incident prediabetes to the best of my knowledge.

Objectives: The purpose of this study was to investigate the relationship between muscle strength, body composition, and incident prediabetes among adults. I, therefore, conducted studies in two different populations with the specific objectives outlined below.

Summary of study 1

Objective: To examine the longitudinal relationship of handgrip strength, a measure of muscle strength, with incident prediabetes among adults in Japan.

Methods: This was a cohort study instituted under the Center of Innovation (COI) program of Japan, aiming to improve the population's health status. The study was conducted in Ibaraki prefecture, whose capital city, Mito, is situated about 125 kilometers north-east of Tokyo. Most of the study participants belonged to the Japan Agriculture Cooperative of Ibaraki (JA Ibaraki). Participants were invited to attend annual medical examinations organized in partnership with JA at the regional hospital (Mito-Kyodo Hospital) and outreach services in the area or attend medical examinations organized by employers, with an annual attendance of 5000 individuals.

The study recruited individuals without prediabetes and diabetes attending lifestyle-related medical examinations between April 2016 and March 2017 (n = 2054). A standardized self-administered questionnaire of 22 items recommended by the Japan Ministry of Health, Labor, and Welfare was used to collect lifestyle-related information and medical history. After that, anthropometric measures, blood pressure fasting blood samples, and handgrip strength measures were taken. Individuals who came for the follow-up medical examinations between April 2018 and March 2019 were included in the analysis (n = 1075).

Results: One hundred sixty-nine individuals (15.7%) developed prediabetes after a mean follow-up of 24.2 months (SD = 1.9 months). Multivariable adjusted hazard ratios (aHR) of new prediabetes cases were calculated using Cox regression. Higher baseline relative handgrip strength predicted a lower risk (aHR [95% CI] = 0.38 [0.21–0.71] of prediabetes incidence among adults. Importantly, relative handgrip strength predicted new prediabetes cases among normal-weight individuals (aHR [95% CI] = 0.39 [0.16–0.96]).

Summary of study 2

Objective: To assess the association of body composition, muscle strength, and quality with prediabetes and T2DM among adults in Malawi.

Methods: This was a cross-sectional study nested in a follow-up study of prediabetic and prehypertensive individuals identified during an extensive NCDs survey in Malawi, which enrolled adults from two defined geographical areas within Karonga District and Lilongwe city. The Malawi Epidemiology and Intervention Research Unit (MEIRU) conducted the baseline NCDs survey between May 16, 2013, and Feb 8, 2016. In the follow-up study, participants were interviewed, had anthropometry, handgrip strength, blood pressure measured, and had fasting blood samples collected. A total of 261 participants were recruited between November 2018 and February 2019.

Results: The mean (SD) age of participants was 49.7 (13.6) years, and 54.0% were between 40 and 59 years. The mean (SD) absolute handgrip strength and relative handgrip strength were 28.8 (7.3) kg and 1.16 (0.40) kg/BMI, respectively, and the mean relative handgrip strength differed significantly *(p*<0.001*)* by T2DM status. Relative handgrip strength was well correlated with anthropometric and body composition measures such as waist circumference (r=-0.510, *P*<0.001), hip circumference (r=-0.572, *P*<0.001), body fat (r=-0.501, *P*<0.001), muscle mass (r=-0.521, *P*=<0.001), and muscle quality (r=0.215, *P*=0.037). In the unadjusted model, the odds ratio (OR) of prediabetes and T2DM per unit increase of relative handgrip strength was 0.12 [95% CI; 0.04-0.33]. The result remained significant after adjusting for age (continuous), sex, place of study, hypertension, dyslipidemia, and level of education (AOR [95% CI]; 0.19 [0.03-0.95]).

Discussion:

This study found that lower baseline relative handgrip strength predicts a higher risk of prediabetes incidence among adults in Japan. This study's important finding was that relative handgrip strength predicted a lower and significant risk of prediabetes incidence among individuals with normal weight (BMI 18.5–24.9 kg/m^2). This study continued to demonstrate this association among participants from the urban and rural areas of Malawi, where it was found that relative handgrip strength is associated with prediabetes and type 2 diabetes mellitus. The findings demonstrated the utility of handgrip strength measurements among sub-Saharan Africa populations.

This simple muscle strength measure is also well correlated with anthropometric and body composition measures among the participants. Additionally, relative handgrip strength was associated with other cardiovascular disease biomarkers. Body mass index alone has a limitation in assessing body composition since it lacks sensitivity for assessing disease risks, especially in people who have normal or mildly elevated BMI. Therefore, handgrip grip strength measurement would provide an opportunity for prediabetes and type 2 diabetes risk screening. Handgrip strength testing is cheap, non-invasive, and is easy to conduct in fieldwork, which would make its adoption in health examinations effortless. Furthermore, like body mass index, participants quickly understood their handgrip strength measurement outcome, which would motivate them to change their lifestyle.

Conclusions:

The use of handgrip strength, a simple measure of muscle strength, may have utility in identifying individuals at high risk of prediabetes who can then be targeted for intervention. Muscle strength may be uniquely important in stratifying prediabetes and type 2 diabetes risk among normal-weight adults considering BMI limitations. Participants of medical examinations could be motivated to improve muscle strength after understanding the risk that lower relative handgrip strength may indicate future prediabetes incidence and risk of type 2 diabetes.

Chapter 1. Overall background

1.1 Global prediabetes and type 2 diabetes mellitus

The global prevalence of type 2 diabetes is rapidly increasing: in 2017, among adults aged 18-99 years, there were 451 million people with diabetes, which was 8.4% of the global adult population, and 5.0 million deaths due to diabetes. The prevalence is expected to rise to 693 million, equaling 9.9% of the adult population by 2045 [1]. Japan is among the countries with the highest prevalence of diabetes mellitus in the world (8.0%–12.1%) [2,3], and the prevalence of diabetes mellitus is increasing rapidly in the Malawi general population, currently estimated at 2.4–6.0% [4,5]. The prevalence of diabetes rises with age such that it reaches 16.0% among those aged 60–64 years in Japan and is as high as 15% in adults aged 50–59 years in Malawi. Furthermore, almost half of people with diabetes were undiagnosed in 2017, and low-income countries had the highest percentage (69.2%) of undiagnosed cases, while the highest number was in middle-income countries. The economic burden of diabetes is also high, with an estimated global cost of US$ 1.31 trillion in 2015, which is 1.8% of the global gross domestic product [6].

Before developing type 2 diabetes, individuals undergo an intermediate phase termed prediabetes, characterized by blood glucose concentrations higher than normal but not high enough to diagnose type 2 diabetes [7–9]. In 2017 there were 374 million people with prediabetes (7.7% of the world population), and most of them lived in low-and middle-income countries [1]. The number of those with impaired glucose tolerance is expected to rise to 587 by 2045. The estimated lifetime risk of progression from prediabetes to type 2 diabetes mellitus in individuals aged 45 years or older is as high as 74.0% [10]. Lifestyle intervention in people with prediabetes may help them revert to normal or delay progression to type 2 diabetes.

Many undiagnosed cases highlight the need to implement screening strategies to identify not only those with diabetes but also those at high risk of diabetes. Most of the cases from low-income countries, especially those in sub-Saharan Africa (SSA), are diagnosed late when individuals report diabetic complications [11]. However, it must be mentioned that there is no evidence that diabetes screening would be effective in diabetes control and management since, to date, no studies have been conducted to demonstrate the cost-effectiveness of screening programs, especially in SSA. Nevertheless, many academics and policymakers maintain that diabetes screening would be beneficial, given the high number of undiagnosed cases.

1.2 Prediabetes, type 2 diabetes mellitus, and muscle strength

Several factors, such as physical inactivity and obesity, are known to increase the risk of type 2 diabetes mellitus and the progression of prediabetes to overt type 2 diabetes mellitus. Recent studies have also examined the role of muscle strength in metabolic conditions. Muscle strength is commonly used to assess overall nutrition, functional capacity, and future disability and is widely used in studies related to aging and frailty [12]. Handgrip strength is a simple measure of muscle strength and has been associated with metabolic syndrome and its components [13,14], type 2 diabetes mellitus [15–17], and overall mortality [18–21]. Handgrip strength has also been associated with hypertension [22], mental health [23], and nutrition status [24]. While most handgrip strength and type 2 diabetes studies were cross-sectional, five were longitudinal, four among both men and women [16,25–27], the other among men only [15]; however, none of these studies were conducted in sub-Saharan Africa.

In an extensive study of normal-weight adults using data from the 2011 to 2012 American National Health and Nutrition Examination Survey, combined handgrip strength was inversely associated with prediabetes among both men and women. However, prediabetes was defined by hemoglobin A1c only, and there was no adjustment for any potential confounders [28]. Another recent study conducted in China reported the cross-sectional association of relative handgrip strength with prediabetes [29]. It is plausible that reduction in muscle strength may precede prediabetes development and that handgrip strength may be used to identify individuals at high risk of prediabetes and type 2 diabetes. This would provide a favorable timing for the implementation of preventive interventions. However, no study had examined the longitudinal relationship between prediabetes and handgrip strength.

Handgrip strength has been associated with incident type 2 diabetes. A recent prospective study of community-dwelling men conducted in Australia found an inverse association between incident type 2 diabetes with grip strength and arm muscle quality [15]. The study was, however, conducted among men only hence not generalizable to women. Similarly, a study conducted among Japanese

Americans found that greater handgrip strength predicted a lower risk of developing type 2 diabetes over ten years in leaner individuals, but the study had a small sample size; hence they could not perform sex-stratified analysis [16]. In Japan, a more extensive cohort study of the longitudinal association between performances on simple physical fitness tests and the incidence of type 2 diabetes mellitus reported that lower relative grip strength (grip strength/body weight) and single-leg balance performance were associated with a higher incidence of type 2 diabetes mellitus among adults aged 20 to 92 years [27].

Several studies have highlighted the importance of skeletal muscle and exercise on glucose deposition and adipose tissue interaction [30–32]. Handgrip strength may be an indicator of muscle strength and quality. However, the underlying mechanism of the observed association is still unclear. One plausible explanation would be that reduction in muscle strength results in insulin resistance. A hypothesis was formulated because of findings suggesting that muscle strength affects the abundance of GLUT-4 receptors involved in insulin-mediated glucose uptake in muscles [30]. Several studies investigating the effects of muscle training exercise have reported significant increases in skeletal muscle GLUT-4 expression and glucose uptake [31,33]. For instance, a randomized clinical trial in Denmark investigated the effects of aerobic exercise training on insulin-stimulated glucose uptake in femoral muscle groups and adipose tissue regions [32]. The study found that aerobic exercise training increased insulin-stimulated glucose uptake in the intervention group but not in their adipose tissue, highlighting the importance of muscle strength training exercises to improve glucose deposition [34].

Studies investigating the biochemical and molecular mechanisms of glucose uptake stimulated by physical exercise in an insulin resistance state have shown that muscle training exercise plays a role as an anti-inflammatory strategy associated with insulin resistance [35]. Mechanistic studies in humans suggest that moderate acute elevations in myokines such as muscle-derived interleukin-6 (IL-6), as provoked by exercise, exert anti-inflammatory effects. Therefore, each acute bout of exercise has a direct impact on protecting against chronic systemic low-grade inflammation. Regular exercise may also mediate anti-inflammatory effects by protecting against visceral fat accumulation, which contributes more to inflammation [36]. These anti-inflammatory properties might be a common denominator for exercise's protective effect on type 2 diabetes and other metabolic conditions. Muscle strength and quality may be indicative of improved muscle function from regular exercise.

However, there are still conflicting findings on the association of handgrip strength and incident type 2 diabetes. For instance, in one prospective study of healthy and relatively young adults, handgrip strength was not associated with incident type 2 diabetes after a median of 10.5 years of follow-up [26]. This study reported that the association of handgrip strength and type 2 diabetes mellitus was not significant after adjustment with risk scores and emphasized the positive correlation of handgrip strength and body mass index as a possible reason for the results from previous studies. The other prospective cohort study reported no association between handgrip strength and incident type 2 diabetes was conducted among relatively older adults in the Health ABC study [25]. The older age of participants was postulated as the reason for the lack of significant results in the Health ABC study. In addition, there are no studies investigating the association of muscle strength with prediabetes and type 2 diabetes in populations in the sub-Saharan Africa region.

1.3 Scientific rationale of the study

Early intervention in prediabetic individuals significantly reduces the risk of progression to type 2 diabetes mellitus. Identifying individuals at higher risk of prediabetes would provide the best opportunity for the implementation of preventive strategies. While much has been studied about obesity-related risk factors, low muscle strength has recently been suggested as a risk factor for type 2 diabetes mellitus. However, some studies did not find such an association, while others suggest reverse causation. Therefore, I conducted two studies, one in Japan and the other in Malawi, to investigate this relationship. The first study in Japan has the potential of providing evidence that reduction in muscle strength precedes the development of both prediabetes and type 2 diabetes. The findings would position muscle strength measurement among the early indicators of prediabetes and type 2 diabetes mellitus risk in the population.

The study in Malawi has the potential of providing preliminary evidence on the utility of handgrip strength in prediabetes and type 2 diabetes screening programs. Despite the rapidly increasing NCD epidemic in SSA, particularly diabetes and hypertension, these conditions remain undetected in most individuals. For example, population surveys have revealed that 73% of people with hypertension and 50 percent of those with diabetes had not been previously diagnosed [11,37]. Therefore, it is crucial to find appropriate low-cost screening interventions to improve detection and increase access to care for patients with NCDs in Africa. Traditional screening approaches rely on age and BMI, but these on their own may not be optimal for SSA, where the significant proportion of individuals with diabetes or hypertension are young and not necessarily overweight or obese. Combined with a very young population, the different origins mean that nearly 50% of individuals with diabetes cannot be identified as high risk by age or BMI [5].

Studies, mostly from high-income countries, have reported that handgrip strength, a simple measure of muscle strength and quality, is associated with type 2 diabetes mellitus. The current evidence suggests that handgrip strength may be a relatively cheap and non-invasive screening tool. However, the utility of handgrip strength measurement in settings of LMIC, and SSA, is unknown.

Importantly, unlike among western populations, prediabetes and type 2 diabetes risk are high among normal-weight individuals in both Japan and Malawi. Therefore, examining other risk states such as low muscle strength may have merit in such populations.

1.4 Research objectives

The present study hypothesized that a reduction in muscle strength precedes prediabetes and type 2 diabetes among adults. Handgrip strength is a simple measure of muscle strength was therefore expected to predict new prediabetes among adults. Handgrip strength was also expected to be associated with type 2 diabetes. This study's main objective was to examine the relationship between muscle strength, body composition, and incident prediabetes among adults. The study purposes were achieved through conducting studies in different populations with the following specific objectives.

1.5 Outline of this thesis

The first study was titled, "**Relative handgrip strength predicts incident prediabetes among adults in Japan: a prospective cohort study**." It aimed to examine the longitudinal relationship of handgrip strength, a measure of muscle strength with incident prediabetes among adults in Japan. The study was a longitudinal study conducted in Ibaraki prefecture, Japan, and recruited individuals without prediabetes and type 2 diabetes mellitus attending lifestyle-related medical examinations between April 2016 and March 2017 (n = 2054).

While the second study titled, "**Association of type 2 diabetes, prediabetes, and muscle strength among adults in Malawi**", aimed at assessing the association of body composition, muscle strength, and quality with prediabetes and T2DM among adults in Malawi. This was a cross-sectional study nested in a cohort study called “Progress of Disease in Prediabetic and Prehypertensive Patients in Malawi: Assessment of Risk Factors and Complications,” which aimed to follow 900 prediabetes and prehypertensive participants identified during the Malawi Epidemiology and Intervention Research Unit (MEIRU) non-communicable diseases (NCDs) survey conducted in Malawi between May 16, 2013, and Feb 8, 2016.

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Chapter 2: Relative handgrip strength predicts incident prediabetes among adults in Japan: a prospective cohort study

2.1 Abstract

Background: Conventional risk factors for prediabetes and type 2 diabetes such as obesity do not completely explain the higher prevalence of prediabetes; therefore, research to investigate the role of other independent risk factors is required. A few cross-sectional studies have reported an association between muscle strength and prediabetes among normal-weight adults, but the longitudinal relationship of muscle strength with incident prediabetes among adults has not been reported. This prospective cohort study was conducted to investigate whether relative handgrip strength in adults predicted prediabetes incidence after 2 years of follow-up.

Methods: The study was conducted in Ibaraki prefecture, Japan, and recruited individuals without prediabetes and diabetes attending lifestyle-related medical examinations between April 2016 and March 2017 (n = 2054). Individuals who came for the follow-up medical examinations between April 2018 and March 2019 were included in the analysis (n = 1075; women: 44.8%).

Results: One hundred sixty-nine individuals (15.7%) developed prediabetes after a mean follow-up of 24.2 months (SD = 1.9 months). Multivariable adjusted hazard ratios (aHR) of new prediabetes cases were calculated using Cox regression. Higher baseline relative handgrip strength predicted a lower risk (aHR [95% CI] = 0.38 [0.21–0.71] of prediabetes incidence among adults. Importantly, relative handgrip strength predicted new prediabetes cases among normal-weight individuals (aHR [95% CI] = 0.39 [0.16–0.96]).

Conclusion: The findings suggest that handgrip strength measurement may help identify individuals at high risk of newly diagnosed prediabetes, importantly, among normal-weight individuals. The identified individuals may benefit from early intervention to reduce the risk of prediabetes.

2.2 Introduction

There were 451 million people with diabetes and 5 million deaths due to diabetes in 2017, with this prevalence expected to rise to 693 million by 2045 [1]. Before developing type 2 diabetes, individuals undergo an intermediate state termed prediabetes, characterized by blood glucose concentrations higher than normal but not high enough for diagnosis [2, 3]. Japan is among the countries with a high prevalence (15%–35%) of prediabetes [4, 5]. Individuals with prediabetes defined as impaired glucose tolerance, impaired fasting glucose, or raised hemoglobin A1c (HbA1c) have a high risk of composite cardiovascular events, coronary heart disease, stroke, and all-cause mortality [6]. Furthermore, the lifetime risk for individuals with prediabetes years to progress to diabetes may be as high as 74·0% among individuals aged 45 years. Early intervention in prediabetic individuals significantly reduces the risk of progression to type 2 diabetes [7], but identifying individuals at higher risk of prediabetes would provide the best opportunity to implement preventive strategies.

While conventional factors such as obesity are well studied, they do not entirely explain the higher prediabetes prevalence observed in Japan, which has a lower rate of obesity than those of western populations [8]. Therefore, other independent risk factors may explain the high prevalence. For instance, it is postulated that Japanese and other Asians have a limited innate ability of insulin secretion and have lower insulin sensitivity, making them more susceptible to insulin resistance with small changes in body composition [9,10]. Studies are required to clarify prediabetes and type 2 diabetes' pathogenesis among such populations to formulate preventive programs that incorporate new messages on the identified independent risk.

Handgrip strength, a simple measure of muscle strength that is well correlated with other strength measures such as quadriceps strength [11], was reported to be associated with metabolic syndrome [12–14], type 2 diabetes mellitus [15–18], and overall mortality [19–21]. While the underlying mechanism has not been well explained, studies exploring the role of muscle resistance exercises in glucose metabolism have reported that such muscle-strengthening activities improve muscle function and glucose deposition [21, 22]. Furthermore, such studies have shown that the impact of exercise training favors insulin-mediated glucose uptake in skeletal muscle rather than in adipose tissue [24]. The results of these studies suggest that muscle strength (a proxy measure of muscle quality) may be an important factor in the development of prediabetes and type 2 diabetes.

However, the longitudinal relationship of handgrip strength with newly diagnosed prediabetes has not been reported. Therefore, whether handgrip strength can be used to identify individuals at high risk of prediabetes who would benefit from early interventions is unknown. Additionally, the association between handgrip strength and type 2 diabetes has not been consistently reported [24, 25], with some studies reporting no association and others suggesting that the observed association results from reverse causation. The confounding effect of body size has been cited as one reason for the conflicting findings; hence, relative handgrip strength has been recommended as a better indicator for considering both the effect of body mass and muscular strength [27]. Therefore, this study was conducted to investigate whether relative handgrip strength predicted prediabetes incidence among adults participating in annual medical examinations in Japan after 2 years of follow-up.

2.3 Methods

Study area and population

The present study was instituted under the Center of Innovation (COI) program of Japan, aiming to improve the population's health status. The study was conducted in Ibaraki prefecture, whose capital city, Mito, is situated about 125 kilometers north-east of Tokyo. Most of the study participants belonged to the Japan Agriculture Cooperative of Ibaraki (JA Ibaraki). Participants were invited to attend annual medical examinations organized in partnership with JA at the regional hospital (Mito-Kyodo Hospital) and outreach services in the area or attend medical examinations organized by employers, with an annual attendance of 5000 individuals. Annual medical examinations are conducted along with the Japanese Industry Safety and Health Act [28] and are performed to facilitate lifestyle change and early disease diagnosis, lower health expenditure, and improve life quality.

This prospective study recruited individuals without prediabetes and diabetes who performed handgrip strength measurement during lifestyle-related medical examinations at a regional hospital and outreach sites between April 2016 and March 2017 (n = 2054). Individuals who were aged younger than 20 (n = 10) or older than 75 years (n = 37); or had handgrip strength measured in one hand or while seated (n = 6); or had a history of stroke (n = 18), heart disease (n = 31), chronic renal failure (n = 6) at baseline were excluded from the study. Some individuals met more than one of the exclusion criteria. Persons were followed up between April 2018 and March 2019, with 1075 (54.7%) individuals attending the 2-years follow-up medical examinations (men: 55.2%; age, mean [SD]: 42.2 [12.7] years). Participants who attended follow-up medical examination within one year after baseline examinations were not included in this analysis. Figure 2.1 shows the flowchart of the participants.

This study was reviewed and approved by the ethics review committee of the University of Tsukuba. It was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

Measures and definitions

Anthropometric measurements such as body weight (kg) and height (cm) using a Tanita DC250 (TANITA Co, Japan), waist circumference (cm), and blood pressure (mmHg) were performed at the regional hospital or the outreach medical examination by trained personnel. Fasting blood samples were collected, and biochemical tests including hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were conducted at the regional hospital laboratory.

Body mass index (BMI; calculated as weight/height^2) was categorized as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30 kg/m^2). Hypertension was defined as any of the following: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication, while dyslipidemia was defined as triglycerides ≥150 mg/dL, LDL-cholesterol ≥140 mg/dL, HDL-cholesterol <40 mg/dL, or self-reported use of anticholesteremic agents [29].

Handgrip strength

Handgrip strength was assessed using a Smedley digital handgrip test machine (Takei Corporation, Japan) following standard operating procedures [30]. The participants were instructed to stand upright and to look straight ahead. The dynamometer handle was adjusted to ensure a comfortable fit. The participants were then told to hold the handle in hand to be tested, with arms straight down by the sides of the body but not touching it or any other object. The participants were instructed to squeeze the dynamometer with a maximum isometric effort for about 5 seconds, and no other body movements were allowed. Handgrip strength was measured twice in each hand, and the average of the maximum handgrip strength values (kg) from each hand was displayed in the machine and used for our analysis.

Relative handgrip strength

Relative handgrip strength was calculated as absolute handgrip strength (kg) divided by BMI (reported as kg/BMI). The use of relative handgrip strength over absolute handgrip strength has been proposed to adjust the direct relationship between mass and force [27]. Absolute handgrip strength is indicative not only of muscle quality but also of the combined effect of fat mass and muscle mass. This was also observed in our data showing that while overweight and obese individuals may have a higher absolute handgrip strength, their relative handgrip strength is lower than normal-weight individuals. This is shown in Figure 2.2.

Prediabetes and type 2 diabetes mellitus

Prediabetes was defined as one or a combination of the following blood glucose results: HbA1c of 5.7% to 6.4% or FPG of 110 to 125 mg/dL [2]. Type 2 diabetes mellitus was defined as any of the following: physician's diagnosis, use of anti-diabetic medication, FPG $\geq$ 126 mg/dL, or HbA1c $\geq$ 6.5%.

Lifestyle and medical history

A standardized self-administered questionnaire of 22 items recommended by the Japan Ministry of Health, Labor, and Welfare was used to collect lifestyle-related information and medical history [31]. It included questions on current smoking (smoking in the past month) and weight change in the past year (±3 kg), regular physical activity (exercising ≥30 minutes per session, ≥2 times per week for ≥1 year, or daily walking or physical activity equal to walking ≥1 hour per day), and alcohol consumption frequency (rarely, sometimes, or every day). The questionnaire included the medical history of type 2 diabetes mellitus, hypertension, heart disease, stroke, renal failure, cancer, and anemia. It also asked about the use of antihypertensive, antidiabetic, and anticholesteremic agents.

Statistical analyses

Participants' baseline demographics, anthropometrics, and lifestyle characteristics were reported as mean values with standard deviations (SD) or median values with interquartile ranges for continuous variables and percentages for categorical variables. Continuous and categorical variables were analyzed using the *t*-test and chi-square test, respectively. Mean biomarker values were presented by sex to show the cardiovascular risk differences between men and women among our study participants. After that, the ANOVA test was used to analyze the mean biomarkers values within age and sex-adjusted tertiles of relative handgrip strength. Skewed variables such as triglycerides, γ-glutamyl transferase, and alanine transaminase were log-transformed, and their geometric means and standard deviations were presented.

I calculated the follow-up period in months from the date of the baseline medical examination to the date of diagnosis of prediabetes at the follow-up medical examination or the last medical examination date. Cox proportional hazards regression analysis was conducted to assess whether baseline relative handgrip strength predicted prediabetes incidence. The analysis was firstly performed among all participants. After that, stratified analyses were performed with age (<40 or ≥40 years) and BMI (18.5–24.9 or ≥25.0 kg/m^2). The stratified analyses with BMI were conducted to assess whether relative handgrip strength predicted the risk of newly diagnosed cases among normal-weight individuals who made up most of our study participants.

Further multivariable-adjusted Cox regression analysis was conducted for the risk of new prediabetes cases within tertiles of age and sex-adjusted relative handgrip strength. Hazard ratios were reported with 95% confidence intervals at a .05 significance level. Variance inflation factors (VIFs) were used to assess multicollinearity, and the VIF values of the fitted models were below 3 (Appendix 1.0). The models were adjusted for body composition, lifestyle characteristics, and other metabolic disease factors. Model 1 was adjusted for age and sex only. Model 2 was adjusted for age, sex, current smoking, dyslipidemia, alcohol consumption frequency, and hypertension. Model 3 was adjusted for the same variables as those in model 2 but included further adjustment for regular physical activity. Additionally, an analysis was conducted to test any interaction between relative handgrip strength and regular physical activity.

Finally, a sensitivity analysis was conducted using multiple imputed datasets. This was done since 4.4 % missing data were observed on some covariates (smoking status, alcohol consumption, and regular physical activity). The multiple imputations were conducted with chained equations, which are widely used [32]. In addition, the models were further adjusted for baseline fasting plasma glucose. Furthermore, I performed a receiver-operating characteristic (ROC) analysis for the models to compare relative handgrip strength and BMI in predicting prediabetes incidence. Also, absolute handgrip strength was investigated if it predicted incident prediabetes among men and women.

All statistical analyses were conducted with SPSS version 24 (IBM, USA) and R statistics version 3.5.2.

2.4 Results

During a mean follow-up period of 24.2 months (SD = 1.9 months), 169 (15.7%) of the 1075 normoglycemic individuals at baseline developed prediabetes, and women had a lower prediabetes incidence (14%) compared to men (17%). The baseline demographics and anthropometric and lifestyle characteristics are shown in Table 2.1. The mean (SD) age and BMI of the participants at baseline were 42.2 (12.7) years and 22.8 (3.5) kg/m^2, respectively. The women were relatively older than the men at baseline (43.7 ± 13.0 vs. 41.0 ± 12.3 years, $P = 0.001$). Higher proportions of the participants were within the age groups of 20 to 39 (44.9%) and 40 to 59 years (44.8%), while only a few (10.3%) individuals were aged older than 60 years. The proportion of underweight women was higher than that of men (14.7% vs. 3.2%, $P < 0.001$), and the proportion of overweight or obese men was higher than that of women (30.0% vs. 15.8%, $P < 0.001$). There was a positive correlation between BMI and absolute handgrip strength among both women (r=0.165, P<0.001) and men (r=0.261, P<0.001). The mean (SD) absolute handgrip strength and relative handgrip strength were 32.8 (9.8) kg and 1.5 (0.4) kg/BMI, respectively, and the relative handgrip strength peaked among individuals aged between 30 and 40 years.

Men and women differed significantly in terms of mean values of waist circumference (83.6 ± 8.9 vs 77.4 ± 10.1 cm, $P < 0.001$), systolic blood pressure (129.3 ± 16.3 vs 121.7 ± 18.1 mmHg, $P < 0.001$), diastolic blood pressure (79.5 ± 12.1 vs 73.1 ± 12.0 mmHg, $P < 0.001$), HDL cholesterol (55.7 ± 13.6 vs 67.3 ± 15.1 mg/dL, $P < 0.001$), LDL cholesterol (119.5 ± 30.9 vs 114.3 ± 30.0 mg/dL, P =0.006), triglycerides (median [IQR]: 93.0 [65.0–138.0] vs 67.0 [50.0–92.0] mg/dL, $P < 0.001$), and creatinine (0.9 ± 0.1 vs 0.6 ± 0.1 mg/dL, $P < 0.001$), with women tending to have healthier cardiovascular biomarker values (Table 2.2)**.** The differences were still observed in age stratified analysis (≤50 and >50 years) conducted to control for pre-menopausal protective effect of estrogen, except for LDL-cholesterol where women aged >50 years had higher but not significant values (124.0 ± 29.6 vs 128.2 ± 29.1 mg/dL, P =0.200) (Appendix 2.0).

Compared with the lower tertile of age and sex-adjusted relative handgrip strength, the middle and higher tertiles were significantly associated with more favorable waist circumference (P < 0.001), systolic blood pressure (P = 0.012), diastolic blood pressure (P = 0.016), total cholesterol (P = 0.004), HDL-cholesterol (P < 0.001), LDL cholesterol (P < 0.001), non-HDL cholesterol (P < 0.001), and triglycerides (P < 0.001). The results of the mean biomarker values of age and sex-specific tertiles of relative handgrip strength are shown in Table 2.3.

The relationship of baseline relative handgrip strength analysis and prediabetes incidence after 2 years of follow-up are shown in Table 2.4. A unit increase in relative handgrip strength predicted a lower and significant risk of prediabetes incidence among all the participants (adjusted hazard ratio, aHR [95% CI] = 0.40 [0.21–0.71]) after adjusting for age (continuous), sex, current smoking, dyslipidemia, alcohol consumption frequency, and hypertension in model 2. Moreover, the results remained significant even after further adjustment for regular physical activity in model 3 (aHR [95% CI] = 0.38 [0.21–0.71]), while no significant interaction was found between relative handgrip strength and regular physical activity.

In stratified analyses, similar and significant results were observed among individuals younger than 40 years (aHR [95% CI] = 0.25 [0.08–0.72]) and those 40 years or older (aHR [95% CI] = 0.45 [0.21–0.95]) after adjusting for age (continuous), sex, current smoking, dyslipidemia, alcohol consumption frequency, hypertension and regular physical activity. Importantly, a unit increase in relative handgrip strength predicted a lower and significant risk (aHR [95% CI] = 0.39 [0.16–0.96]) of prediabetes incidence among individuals with normal BMI (18.5–24.9 kg/m^2). Furthermore, a lower but not significant risk (aHR [95% CI] = 0.75 [0.25–2.26]) was also observed among those with BMI ≥ 25.0 kg/m^2 after adjusting for age (continuous), sex, current smoking, dyslipidemia, alcohol consumption frequency, hypertension, and regular physical activity.

Additional analysis using sex and age-adjusted tertiles of relative handgrip strength produced similar results (Table 2.5). Compared with those in the lower tertile of relative handgrip strength, lower risk of prediabetes incidence was observed among those in the middle (aHR [95% CI] = 0.61 [0.42–0.87]) and upper tertiles (aHR [95% CI] = 0.59 [0.40–0.86]). Sensitivity analysis using multiple imputed data showed comparable results with analyses using complete-case analysis even when baseline fasting plasma glucose was considered (Table 2.6). In sensitivity analysis using absolute handgrip strength, lower risk of prediabetes incidence was observed among men in the upper (aHR [95% CI] = 0.55 [0.31–0.98]) and middle tertiles of absolute handgrip strength (aHR [95% CI] = 0.94 [0.56–1.59]) compared to those in the lower tertile. Similarly, women in the upper (aHR [95% CI] = 0.71 [0.36–1.40]) and middle (aHR [95% CI] = 0.82 [0.43–1.55]) tertiles of absolute handgrip strength had lower risk of incident prediabetes compared to those in the lower tertile. However, the results in women did not reach statistical significance. ROC analysis for the models showed that overall, the relative handgrip strength model performed similarly to the BMI model (AUC [95% CI] = 0.698 [0.658–0.738] vs. 0.695 [0.654–0.736] but the relative handgrip strength model was slightly better among normal-weight individuals (AUC [95% CI] = 0.702 [0.654–0.751] vs. 0.695 [0.646–0.743].

2.5 Discussion

This study examined whether relative handgrip strength predicts incident prediabetes among a sample of Japanese adults attending annual medical examinations. Fifteen percent of individuals had incident prediabetes within 2 years of follow-up, suggesting a high risk of prediabetes among the participants. The high prediabetes incidence is similar to an earlier incidence rate (17%) reported in a Japanese population using both HBA1c and fasting plasma glucose for diagnosis [2]. The current study population could benefit from lifestyle and pharmacological interventions known to have a preventive effect on prediabetes's progression to type 2 diabetes [7]. This study found that lower baseline relative handgrip strength predicted a higher risk of prediabetes incidence among the participants. This study's important finding was that relative handgrip strength predicted a lower and significant risk of prediabetes incidence among individuals with normal weight (BMI 18.5–24.9 kg/m^2). This was also shown in Receiver-operating characteristic (ROC) analysis comparing relative handgrip strength and BMI models, which found that the relative handgrip strength model performed best among normal-weight individuals. The use of handgrip strength, a simple measure of muscle strength, may have utility in identifying individuals at high risk of prediabetes who can then be targeted for intervention. Participants of annual medical examinations could be motivated to improve muscle strength after understanding the risk that lower relative handgrip strength may indicate for future prediabetes incidence and risk of type 2 diabetes.

A positive correlation between BMI and absolute handgrip strength was observed among both women and men; therefore, normalizing HGS by BMI was necessary. However, the distribution of absolute handgrip strength and relative handgrip strength with BMI is different among men and women. This could be because women in this study are mostly normal weight and have a narrow distribution of handgrip strength. Moreover, women in this study have better cardiovascular diseases profile as well, and their prediabetes incidence is lower (14%) compared to men (17%). This may be why the results of the association of absolute handgrip strength and incidence of prediabetes were not significant in women. Further studies are required to clarify this association.

This is the first study to report the impact of handgrip strength on prediabetes incidence after 2-years of follow-up. It extends the findings on the cross-sectional association of relative handgrip strength with fasting blood glucose [27], prediabetes [34, 35], and incident type 2 diabetes [18]. Relative handgrip strength was also associated with several cardiovascular biomarkers in our study, similar to findings from an earlier study [27]. Prediabetes is associated with higher cardiovascular risk [6]; therefore, simple indicators combining various risk states such as relative handgrip strength may have utility in screening and intervention programs for both conditions in the community.

The findings suggest that reduction in muscle strength may precede the development of prediabetes, thereby providing a favorable window where meaningful intervention programs can be implemented. In addition, interventions targeted to high-risk individuals may result in more individuals taking part in community self-exercise campaigns, which we believe would benefit this community. Some simple exercises, such as elastic resistance training that can be performed at home, are already known to improve muscle strength and functional performance [35].

The current study shows that relative handgrip strength may be used to stratify prediabetes risk among populations with lower rates of obesity, such as Japan, where a higher risk of prediabetes and type 2 diabetes is observed even in individuals with normal body mass index [4, 36]. Indeed, baseline relative handgrip strength predicted newly diagnosed prediabetes cases among individuals with normal weight (BMI 18.5–24.9 kg/m^2). This is, to my knowledge is the first study to report such findings. The association was, however, not significant among overweight and obese individuals in this study. While the result may be due to the smaller number of individuals with BMI ≥ 25.0 kg/m^2 in the current study, a few studies investigating the association of muscle mass and metabolic syndrome reported significant results only in non-obese individuals in Asia. Several explanations have been suggested, including that muscle mass may have a lesser impact because of pre-existing imbalances in obese participants [37]. The greater the fat content in skeletal muscle disrupts glucose metabolism since it is associated with reduced insulin sensitivity.

Additionally, BMI does not distinguish between fat mass and fat-free mass, which may contribute to the failure to detect a significant association in the overweight/obese stratum since fat mass contribution to muscular strength is minimal compared to fat-free mass (FFM). Studies are required to investigate further the association of relative handgrip strength with incident prediabetes among overweight and obese individuals. These studies may explore the use of fat-free mass in the denominator of the strength metric (kg/kgFFM).

These findings also suggest that muscle strength may play a role in the development of prediabetes. While the underlying mechanism has not been well explained, physiological research suggests potential causal pathways and muscle strength benefits. For example, muscle strength affects the abundance of GLUT-4 receptors involved in insulin-mediated glucose uptake in muscles [24], and several studies investigating the effects of muscle training exercise have reported significant increases in skeletal muscle GLUT-4 expression and glucose uptake [21, 37]. However, the present study found that the association between relative handgrip strength and incident prediabetes was still significant even after adjusting for regular physical activity. A finding suggesting that this association may be independent of regular physical activity or that resistance exercises are not well highlighted in the standard regular physical activity questionnaire implemented in the annual medical examinations, thereby necessitating the inclusion of handgrip strength in these examinations to ascertain the muscle function capacity of participants fully.

This study's strength was the broad age range of the individuals attending the annual medical examinations, which enables its generalizability with age. This advantage is lost when dealing with similar assessments conducted among company working individuals in which the age range is narrow. Also, the use of both hemoglobin A1c and fasting plasma glucose may have increased our ability to detect individuals with prediabetes [2, 38]. Finally, these annual medical examinations are open not only to farmers but also to their dependents and nonfarming community members, making the community's data representative.

Limitations

The present study has some limitations. Firstly, an oral glucose tolerance test (OGTT), which is used to identify individuals with impaired glucose tolerance, was not performed, which may have resulted in the misclassification of some individuals. Selection bias is also possible since we used data from individuals taking annual medical examinations who may be more health-conscious than the general population. Furthermore, most individuals join medical examinations at an average of 1.5 years; therefore, some participants did not come for medical examinations during the 2018 fiscal year. However, the age and sex distributions of those who did not participate in the 2-year follow-up were comparable to those who came for the follow-up examinations. The study also followed up the participants for 2 years only, which may not be enough time to rule out reverse causation; however, the present study results still have utility in the identification of individuals at high risk of prediabetes in medical examinations who may benefit from early interventions. The study had no information on family history of type 2 diabetes and, therefore, did not adjust for genetic influence. Lastly, while we excluded participants with stroke, heart disease and adjusted for other conditions such as dyslipidemia and hypertension, residual confounding cannot be completely ruled out.

Further studies are required to examine muscle strength association with incident prediabetes, especially among overweight and obese individuals. Furthermore, studies to identify age-specific cutoff values of relative handgrip strength to identify the target population with a high risk of developing prediabetes are required to facilitate easy interpretation and feedback to participants.

Conclusions

This study found that baseline relative handgrip strength predicts incident prediabetes among adults in Japan. The findings suggest that relative handgrip strength may be used to identify individuals at high risk of prediabetes, especially among normal-weight individuals who may benefit from early intervention to reduce the risk of type 2 diabetes and cardiovascular diseases.

2.6 References

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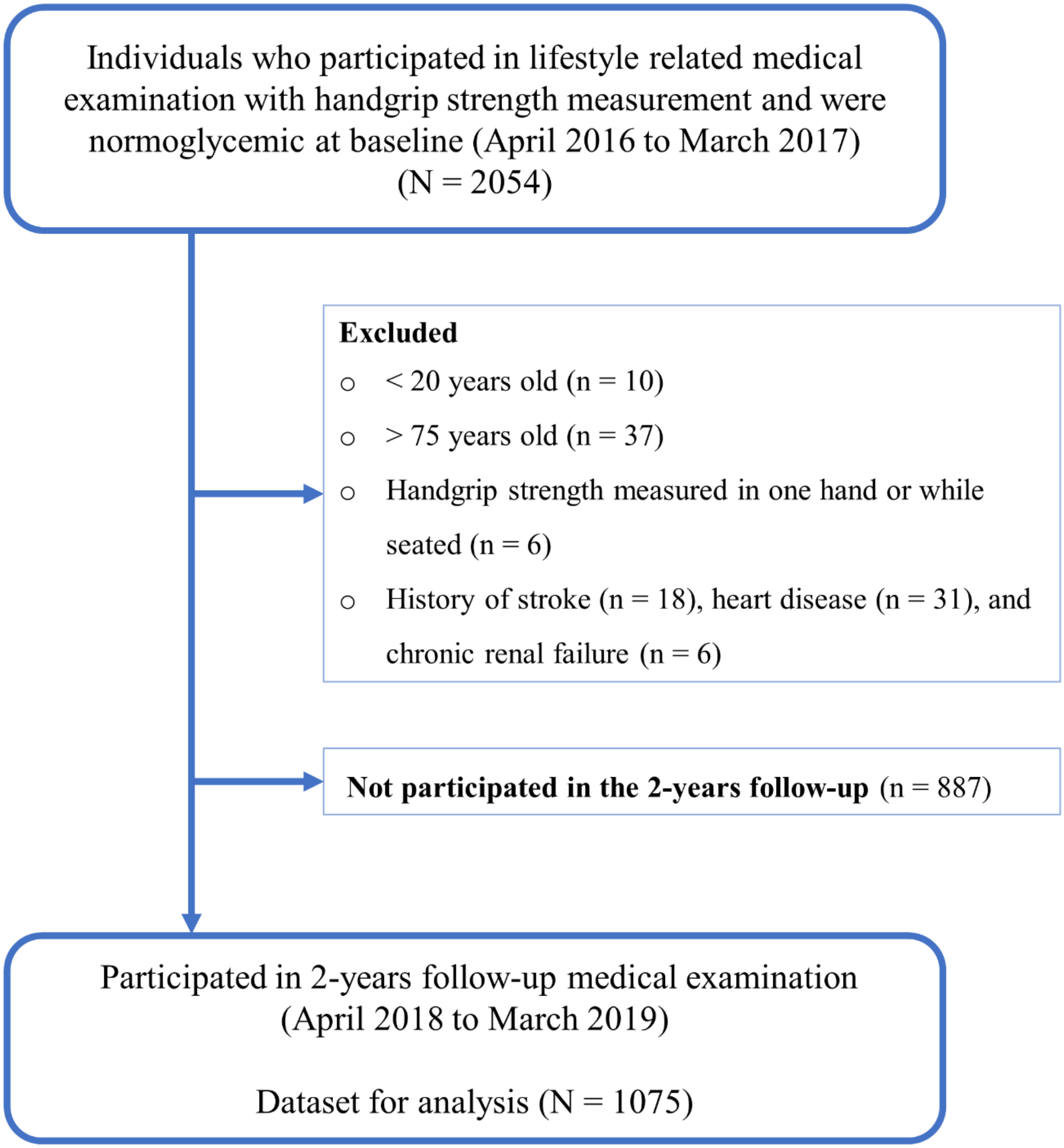

Abbreviations: HbA1c: hemoglobin A1c; FPG: Fasting plasma glucose.

Figure 2.1 Flow-chart of study participants.

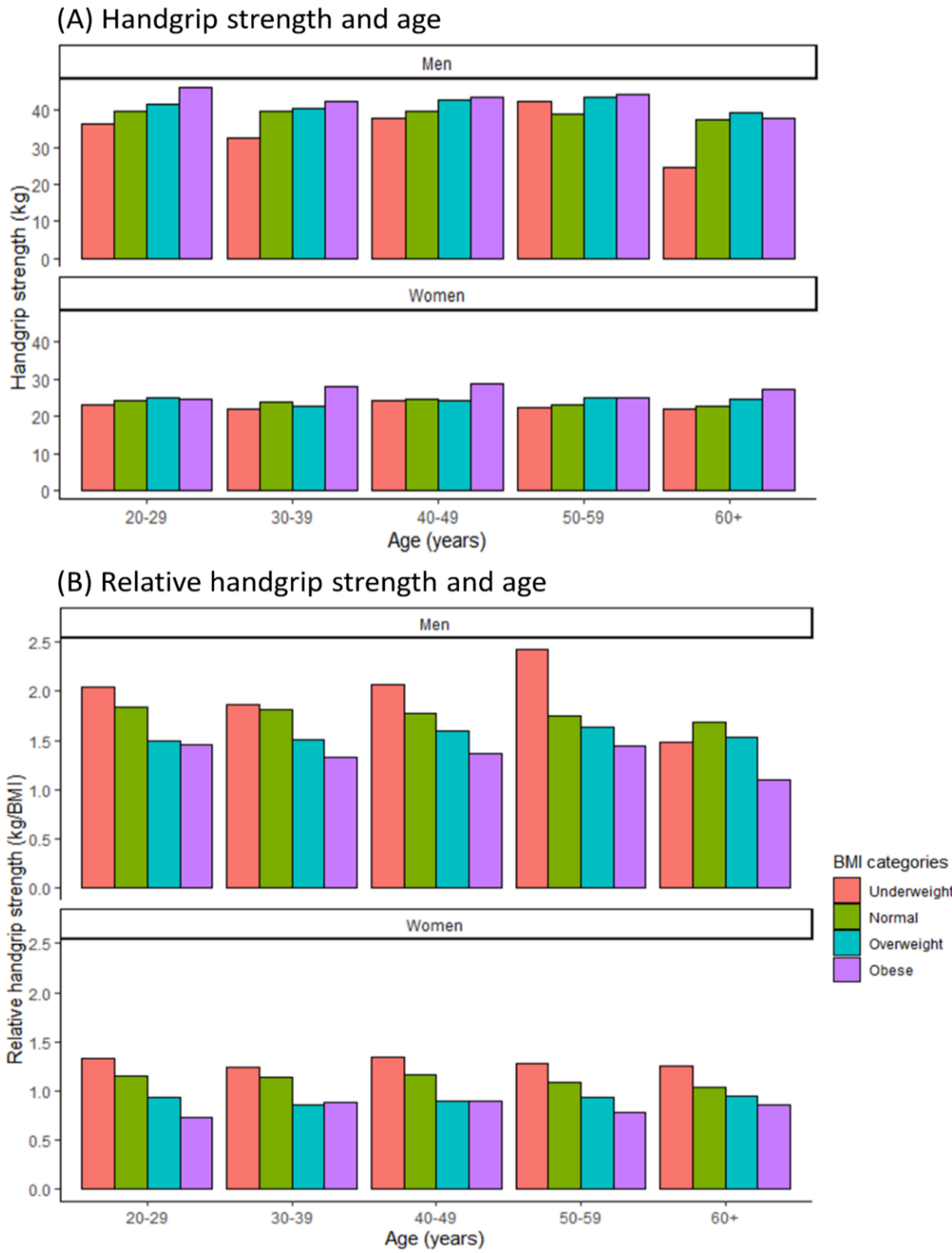

Figure 2.2 Absolute and relative handgrip strength by sex and BMI categories.

Table 2.1 Demographics, anthropometrics, and lifestyle characteristics at baseline.

Characteristic	All n = 1075	Men n = 593 (55.2%)	Women n = 482 (44.8%)
Age (years), mean ± SD	42.2 ± 12.7	41.0 ± 12.3	43.7 ± 13.0
20–39	483 (44.9)	294 (49.6)	189 (39.2)
40–59	482 (44.8)	248 (41.8)	234 (48.5)
60–75	110 (10.3)	51 (8.6)	59 (12.3)
BMI (kg/m^2), mean ± SD	22.8 ± 3.5	23.7 ± 3.3	21.8 ± 3.6
Underweight	90 (8.4)	19 (3.2)	71 (14.7)
Normal	731 (68.0)	396 (66.8)	335 (69.5)
Overweight	208 (19.3)	150 (25.3)	58 (12.1)
Obese	46 (4.3)	28 (4.7)	18 (3.7)
Alcohol consumption frequency [a]			
Rarely	472 (45.9)	205 (36.0)	267 (58.2)
Sometimes	332 (32.3)	200 (35.1)	132 (28.8)
Every day	225 (21.8)	165 (28.9)	60 (13.0)
Regular physical activity [a]			
Yes	340 (33.0)	211 (37.0)	129 (28.1)
No	689 (67.0)	359 (63.0)	330 (68.5)
Current smoking [a]			
Yes	248 (24.1)	192 (33.7)	56 (12.2)
No	781 (75.9)	378 (66.3)	403 (87.8)
Hypertension			
Yes	287 (26.7)	191 (32.2)	96 (19.9)
No	788 (73.3)	402 (67.8)	386 (80.1)
Dyslipidemia			
Yes	379 (35.3)	246 (41.5)	133 (27.6)
No	696 (64.7)	347 (58.5)	349 (72.4)

Abbreviations: BMI: body mass index; Means and standard deviations (SD) are shown for continuous variables, and the number of participants and percentages, for categorical variables. [a]Number of participants = 1029.

Table 2.2 Biomarker values by sex at baseline.

Characteristic		Men n = 593	Women n = 482	*P*-value [b]
Waist circumference	cm	83.6 ± 8.9	77.4 ± 10.1	< 0.001
Systolic blood pressure	mmHg	129.3 ± 16.3	121.7 ± 18.1	< 0.001
Diastolic blood pressure	mmHg	79.5 ± 12.1	73.1 ± 12.0	< 0.001
Total cholesterol	mg/dL	195.4 ± 32.8	199.2 ± 35.4	0.069
HDL cholesterol	mg/dL	55.7 ± 13.6	67.3 ± 15.1	< 0.001
LDL cholesterol	mg/dL	119.5 ± 30.9	114.3 ± 30.0	0.006
Triglycerides [a]	mg/dL	93.0 (65.0 – 138.0)	67.0 (50.0 – 92.0)	< 0.001
Creatinine	mg/dL	0.9 ± 0.1	0.6 ± 0.1	< 0.001
Relative handgrip strength	kg/BMI	1.7 ± 0.3	1.1 ± 0.2	< 0.001

Abbreviations: HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Means and standard deviations are shown for continuous variables and the number of participants and percentages for categorical variables.

[a]Data for triglycerides were skewed and, therefore, presented as median (interquartile range) values and P-values obtained with the Kruskal-Wallis test.

[b]P-values were obtained with the t-test.

Table 2.3 Mean biomarker values by age and sex-specific tertiles of relative handgrip strength at baseline.

Biomarker		Q1 n = 320	Q2 n = 392	Q3 n = 363	*P*-value[b]
Waist circumference	cm	86.0 ± 10.6	80.0 ± 9.0	77.0 ± 8.1	< 0.001
Systolic BP	mmHg	127.9 ± 17.3	126.0 ± 18.4	124.0 ± 16.7	0.012
Diastolic BP	mmHg	78.3 ± 12.2	76.1 ± 13.0	75.7 ± 12.0	0.016
Total Cholesterol	mg/dL	202.3 ± 34.7	196.0 ± 34.1	194.0 ± 32.8	0.004
HDL Cholesterol	mg/dL	58.5 ± 15.0	60.3 ± 15.0	63.7 ± 15.8	< 0.001
LDL Cholesterol	mg/dL	123.8 ± 31.5	116.6 ± 29.3	111.9 ± 30.0	< 0.001
Non-HDL Cholesterol	mg/dL	143.9 ± 34.8	135.5 ± 33.3	130.2 ± 32.9	< 0.001
Triglycerides [a]	mg/dL	91.6 ± 1.7	84.1 ± 1.7	77.1 ± 1.7	< 0.001
Alanine transaminase [a]	IU/L	21.3 ± 1.8	19.1 ± 1.7	16.7 ± 1.5	< 0.001
γ-glutamyl transferase [a]	IU/L	26.8 ± 1.9	25.0 ± 2.0	22.8 ± 1.8	0.005
Albumin	g/dL	4.5 ± 0.3	4.5 ± 0.3	4.6 ± 0.3	0.128

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Means and standard deviations are shown.

[a]Calculated using geometric means and standard deviations.

[b]*P*-values by ANOVA test.

Table 2.4 Adjusted hazard ratios for the risk of new prediabetes cases with increasing relative handgrip strength.

			Model 1[a]			**Model 2[b]**	**Model 3[c]**
	Cases (%)	n	aHR (95% CI)	Cases (%)	n [d]	aHR (95% CI)	aHR (95% CI)
All participants	169 (15.8)	1073	**0.33 (0.18 – 0.60)**	165 (16.1)	1027	**0.40 (0.21 – 0.71)**	**0.38 (0.21 – 0.71)**
Age (years)							
< 40	43 (8.9)	483	**0.27 (0.10 – 0.73)**	43 (9.5)	455	**0.25 (0.09 – 0.74)**	**0.25 (0.08 – 0.72)**
≥ 40	126 (21.3)	590	**0.37 (0.21 – 0.95)**	122 (21.3)	572	**0.47 (0.22 – 0.98)**	**0.45 (0.21 – 0.95)**
BMI (kg/m^2)							
18.5 – 25.0	100 (13.7)	729	**0.37 (0.15 – 0.90)**	98 (14.0)	698	**0.39 (0.16 – 0.95)**	**0.39 (0.16 – 0.96)**
≥ 25.0	61 (24.0)	254	0.66 (0.24 – 1.84)	59 (24.4)	242	0.78 (0.26 – 2.33)	0.75 (0.25 – 2.26)

Abbreviations: aHR, Adjusted hazard ratio; CI, confidence interval.

Boldface indicates statistical significance ($P < .05$).

[a]Model 1: adjusted for age and sex.

[b]Model 2: adjusted for age, sex, dyslipidemia, hypertension, smoking status, and alcohol consumption frequency.

[c]Model 3: model 2 + regular physical activity.

[d]n, only participants with complete information on covariates included in models 2 and 3.

Table 2.5 Adjusted hazard ratios for the risk of new prediabetes cases within tertiles of relative handgrip strength.

	Model 1[a]	**Model 2[b]**	**Model 3[c]**
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
n	1073	1027[d]	1027[d]
Cases (%)	169 (15.8)	165 (16.1)	165 (16.1)
Tertiles			
Lower	1 (reference)	1 (reference)	1 (reference)
Middle	**0.60 (0.47 – 0.86)**	**0.61 (0.42 – 0.88)**	**0.61 (0.42 – 0.87)**
Upper	**0.55 (0.38 – 0.80)**	**0.60 (0.40 – 0.88)**	**0.59 (0.40 – 0.86)**

Abbreviations: aHR, Adjusted hazard ratio; CI, confidence interval.

Boldface indicates statistical significance ($P < 0.05$).

[a]Model 1: adjusted for age and sex.

[b]Model 2: adjusted for age, sex, dyslipidemia, hypertension, smoking status, and alcohol consumption frequency.

[c]Model 3: model 2 + regular physical activity.

[d]Only participants with complete information on covariates included in models 2 and 3.

Table 2.6 Adjusted hazard ratios for the risk of new prediabetes cases with increasing relative handgrip strength (multiple imputed dataset).

			Model 1[a]	**Model 2[b]**	**Model 3[c]**
	Cases (%)	n	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
All participants	169 (15.3)	1073	**0.33 (0.18 – 0.60)**	**0.38 (0.21 – 0.70)**	**0.37 (0.20 – 0.68)**
Age (years)					
< 40	43 (8.9),	483	**0.27 (0.10 – 0.73)**	**0.29 (0.10 – 0.86)**	**0.28 (0.09 – 0.84)**
≥ 40	126 (21.3)	590	**0.37 (0.21 – 0.95)**	**0.41 (0.20 – 0.86)**	**0.39 (0.19 – 0.82)**
BMI (kg/m^2)					
18.5 – 25.0	100 (13.7)	729	**0.37 (0.15 – 0.90)**	**0.39 (0.16 – 0.99)**	**0.39 (0.16 – 0.98)**
≥ 25.0	61 (24.0)	254	0.66 (0.24 – 1.84)	0.67 (0.23 – 1.94)	0.64 (0.22 – 1.86)

Abbreviations: aHR, Adjusted hazard ratio; CI, confidence interval.

Boldface indicates statistical significance ($P < 0.05$).

[a]Model 1: adjusted for age and sex.

[b]Model 2: adjusted for age, sex, baseline fasting plasma glucose, dyslipidemia, hypertension, smoking status, and alcohol consumption frequency.

[c]Model 3: model 2 + regular physical activity.

Chapter 3: Association of type 2 diabetes, prediabetes, and muscle strength among adults in Malawi

3.1 Abstract

Background: The shared risk factors for non-communicable diseases (NCDs), such as obesity, are well reported. However, contrary to data from high-income countries, studies from Sub-Saharan Africa (SAA) show that a substantial proportion of people with diabetes are not overweight or obese. One possible explanation might relate to the limitation of body mass index (BMI) since it lacks sensitivity for assessing disease risks, especially in people with normal or mildly elevated body weight. On the other hand, muscle strength has been reported as a predictor of both prediabetes and type 2 diabetes mellitus (T2DM) in populations outside SSA. Therefore, this study examined the relationship of handgrip strength with prediabetes and T2DM among rural and urban-dwelling adults in Malawi to assess its utility in prediabetes and T2DM screening during medical examinations.

Methods: This was a cross-sectional study nested in a follow-up study of prediabetic and prehypertensive individuals identified during an extensive NCDs survey in Malawi, which enrolled adults from two defined geographical areas within Karonga District and Lilongwe city. Participants were interviewed, had anthropometry, handgrip strength, and blood pressure measured, and had fasting blood samples collected. A total of 261 participants (women: 64%) were recruited between November 2018 and February 2019. Univariate and multivariate binary logistics regression analysis was performed to examine the association of prediabetes and T2DM with relative handgrip strength.

Results: The mean (SD) age of participants was 49.7 (13.6) years, and 54.0% were between 40 and 59 years. The mean (SD) absolute handgrip strength and relative handgrip strength were 28.8 (7.3) kg and 1.16 (0.40) kg/BMI, respectively, and the mean relative handgrip strength differed significantly *(P* <0.001*)* by T2DM status. Relative handgrip strength was well correlated with anthropometric and body composition measures such as waist circumference (r=-0.510, *P*<0.001),hip circumference (r=-0.572, *P*<0.001), body fat (r=-0.501, *P*<0.001), muscle mass (r=-0.521, *P*=<0.001), and muscle quality (r=0.215, *P*=0.037). In the unadjusted model, the odds ratio (OR) of prediabetes and T2DM per unit increase of relative handgrip strength was 0.12 [95% CI; 0.04-0.33]. The result remained significant after adjusting for age (continuous), sex, place of study, hypertension, dyslipidemia, and level of education (AOR [95% CI]; 0.19 [0.03-0.95]).

Conclusions: The findings provide preliminary evidence for adopting handgrip strength during medical examinations in Malawi, given earlier evidence of a high prevalence of diabetes among normal-weight individuals.

3.2 Introduction

Sub-Saharan Africa (SSA) is experiencing a rapid increase in the burden of non-communicable diseases (NCDs) such as diabetes mellitus [1,2] and hypertension. Malawi is one of the SSA countries experiencing the rise of NCDs. A few extensive population-based surveys conducted between 2009 and 2016 found a higher prevalence of hypertension (18.0% to 33.0%) and diabetes mellitus (2.4% to 6.0%) in the Malawi general population [3,4]. The rapid rise has been attributed to urbanization and associated lifestyle changes (such as physical inactivity, poor nutrition, alcohol consumption, smoking, and poor sleep habits), increasing wealth, and rising population age [4].

Therefore, it is necessary to intensify research on the emerging NCDs burden since most of the available literature is from western populations. Notably, 80% of all NCDs mortality happens in developing countries, exacerbated by inadequate health care systems [5]. Effective control of NCDs starts with well-designed screening strategies to identify individuals at high risk and implement intervention programs besides treating individuals with these conditions. The approach is the most cost-effective to control NCDs, considering the high cost of treating these conditions [6,7].

The shared risk factors for NCDs are well studied. However, population-based studies conducted in SSA reveal differences in the contribution of known risk factors on non-communicable disease outcomes compared to high-income countries, and the reasons for the observed differences are unclear [1]. For instance, an increased risk of hypertension and T2DM has been reported among relatively low or normal body mass index (BMI) individuals in Malawi, a setting with high mean adult BMI. [4]. One possible explanation for this discrepancy might relate to factors specific to this setting, including fetal exposure to maternal undernutrition or early childhood malnutrition, which are thought to increase NCDs' susceptibility in adulthood according to the Developmental Origins of Health and Disease hypothesis (DOHaD) [8,9]. The other explanation might relate to BMI limitation in assessing body composition since it lacks sensitivity for assessing disease risks, particularly in people who have normal or mildly elevated body weight [10]. Consequently, current hypertension and diabetes screening guidelines, which focus on overweight, smoking, excess alcohol drinking, family history, and age, may miss some individuals at high risk.

Studies mostly from high-income countries have reported that handgrip strength, a simple measure of muscle strength and quality, is associated with metabolic syndrome [11], type 2 diabetes mellitus [12–14], and overall mortality [15,16]. Therefore, it is conceivable that muscle strength might also be associated with prediabetes and T2DM in Malawi. Handgrip strength testing is cheap, non-invasive, and easy to use in fieldwork, which would make its adoption in prediabetes and type 2 diabetes screening programs easy. However, there is a need for evidence to adopt the use of handgrip strength together with body composition measurements to identify individuals at high risk of T2DM in Malawi. Therefore, this study aimed to examine the relationship of handgrip strength with prediabetes and T2DM among rural and urban-dwelling adults in Malawi.

3.3 Methods

Study design

This cross-sectional study is part of a follow up of the Malawi NCDs survey that provided detailed baseline data on blood glucose regulation by subgroups of age, location (urban vs. rural), and multi-morbidity, and established a research infrastructure to conduct longitudinal follow-up of participants' access to health-care, health outcomes, and vital statistics. The Malawi NCDs survey was conducted in the northern rural Karonga District and Malawi's central capital, Lilongwe. The details of the NCDs survey design and methodology are described in earlier publications [4,17]. The NCDs survey provided an opportunity to conduct a follow-up study on disease progression among prediabetic and prehypertensive individuals identified during the survey.

The follow-up study was called "the progress of disease in prediabetic and prehypertensive patients in Malawi: assessment of risk factors and complication." It was designed to recruit all 388 prediabetic participants and a further random sample of 512 "prehypertensive" participants to determine disease progression in this population. Prediabetes participants were defined according to the WHO classification of a fasting plasma glucose between 6.0 mmol/L and less than 7 mmol/L with no history of diabetes and no history of taking diabetes medication, while prehypertensive participants were defined by systolic blood pressure between 120 to 139 mmHg and/or diastolic blood pressure between 80 to 89 mmHg based on two or more properly measured seated blood pressure readings.

The current cross-sectional study was designed to collect data on muscle strength. A total of 261 participants from both the rural and urban locations were recruited in this current cross-sectional study to assess handgrip strength. This study was reviewed and approved by the ethics committee of the National Health Sciences Research Committee (NHSRC) in Malawi and the University of Tsukuba in Japan.

Study area and population

The urban study site, Area 25 in Lilongwe, is an area with a population of 66,000 individuals of mixed social-economic status with a relatively poor lifestyle compared to the rural population. During the 2008 national population census, there were 24,367 adults aged ≥18 years. This population was targeted for recruitment in the NCDs survey between May 16, 2013, and Feb 8, 2016. Among those targeted in area 25 Lilongwe, 15,013 individuals were recruited. While the rural site, Chilumba Health, and Demographic Surveillance Site (HDSS) in Karonga, is an area with a population of 39,000 individuals, of whom 15,806 were adults aged ≥18 years. These were targeted for recruitment in the survey. Unlike the urban study area, the rural site is a predominantly subsistence economy with farming and fishing as the main economic activities.

Data collection

Participants' information on risk factors for T2DM was extracted for analysis, and this information was collected through a questionnaire partly adapted from the WHO STEPS survey, biophysical measurements, and examination of biological specimens. After that, participants were contacted for follow up visits.

A field team of trained data collectors visited the participants at their respective homes between November 2018 and February 2019 using the contact information collected during the baseline NCDs survey for follow-up purposes. The field team administered an in-depth questionnaire and clinical measurements to reassess the risk factors for T2DM and hypertension. The information collected under the survey included: age, gender, urban/rural residence, occupation, environmental exposures, biophysical profiles, medical history and medication, meat consumption, smoking, and alcohol consumption. After that, the field team measured participants' height, weight, and blood pressure following standardized protocols, as documented in an earlier publication [4].

Handgrip strength was then measured using the Takei handgrip strength machine (Model TKK 5401) following the manufacturer's standard operating procedure. Additionally, the field team measured the bioelectrical impedance (BIA) of participants recruited in Area 25 in Lilongwe using a compact Tanita BIA machine (RD-800). The information recorded included participants' body mass index, body water percentage, bone mass, body fat, muscle quality score, and muscle mass on standard data collection forms sent to the MEIRU data offices for entry.

The field team advised the participants to have an overnight fast of 8 hours to prepare a blood sample collection the following morning. The fasting blood samples were collected to test fasting plasma glucose (FPG), Hemoglobin A1c (HbA1c), low-density lipoprotein (LDL-cholesterol), high-density lipoprotein (HDL-cholesterol), total cholesterol, triglycerides, and creatinine.

Measures and definitions

Body mass index (BMI; calculated as weight/height^2) was categorized as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30 kg/m^2). Hypertension was defined as any of the following: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication, while dyslipidemia was defined as triglycerides ≥150 mg/dL, LDL-cholesterol ≥140 mg/dL, HDL-cholesterol <40 mg/dL. Prediabetes was defined as FPG of 6.1 to 6.9 mmol/L (110 to 125 mg/dL). Type 2 diabetes mellitus was defined as any of the following: physician's diagnosis, use of anti-diabetic medication, FPG ≥7.0 mmol/L (≥126 mg/dL).

Educational attainment was categorized according to the highest level reached. The levels included: those who had attended none, primary school (standards 1-8), secondary school (forms 1-4), or post-secondary education (including vocational training). Employment data was also collected in pre-coded categories and were further grouped into salaried, self-employed, subsistence, housework, and not working [4]. Estimated family monthly income information was summarized using predefined income categories in Malawi Kwacha (1. ≤ MWK 20,000 (26 USD); 2. More than MWK 20,000 and ≤ MWK 100,000 (131 USD); 3. MWK>100,000 (131 USD)). Physical activity information was collected by asking whether the participants performed vigorous work, which caused significant breathing/heart rate increases. Current smokers were those who were still smoking or stopped in the previous six months. Alcohol use was reported as any consumption of alcohol in the past year.

The handgrip strength measurement procedure involved instructing participants to stand upright and to look straight ahead. The dynamometer handle was adjusted to ensure a comfortable fit. The participants were then told to hold the handle in hand to be tested with arms straight down by the sides of the body but not touching it or any other object. The participants were instructed to squeeze the dynamometer with a maximum isometric effort for about 5 seconds, and no other body movements were allowed. Handgrip strength was measured twice in each hand, and the average of the maximum handgrip strength values (kg) from each side was displayed in the machine and used for our analysis.

Relative handgrip strength was calculated as absolute handgrip strength (kg) divided by BMI (reported as kg/BMI). Handgrip strength and BMI are highly correlated [18]. Therefore, the use of relative handgrip strength over absolute handgrip strength has been proposed to adjust for the direct relationship between mass and force [19]. Absolute handgrip strength is not only indicative of muscle quality but also the combined effect of fat mass and muscle mass.

Statistical analyses

Sociodemographic, anthropometric, and lifestyle characteristics were reported as mean values with standard deviations (SD) for continuous variables and percentages for categorical variables. Continuous variables were analyzed using the t-test and ANOVA test, while categorical variables were analyzed using the chi-square test. The characteristics of the participants were presented according to their type 2 diabetes status. Multiple linear regression of relative handgrip strength on selected biomarker outcomes was performed to understand the association of relative handgrip strength with the biomarker outcomes adjusted for age, sex, and study place. After that, the correlation of handgrip strength with body composition measurements was analyzed in a subsample comprising of urban-dwelling participants.

Finally, I performed univariate and multivariate binary logistic regression to examine the association of prediabetes and type 2 diabetes with relative handgrip strength. Individuals with complete information (n=254) were included in the models. The covariates considered in the models were age (continuous), sex, place of study, hypertension, dyslipidemia, and level of education (the four levels of education categories were merged into 2 before including in the models: those with none or primary education were put into one group while those with secondary and post-secondary were combined into another group). Model 1 was adjusted for age, sex, and study place, while Model 2 included hypertension status. The final Model 3 included all variables adjusted for in model 2 and was further adjusted for dyslipidemia and education level. The education level was strongly correlated with employment status and was therefore selected to adjust for socioeconomic status. On the other hand, dyslipidemia was included since it was significantly associated with prediabetes and type 2 diabetes.

Variance inflation factors were used to assess multicollinearity, and the VIF values of the fitted models were below 3 (Appendix 3.0). Odds ratios were reported with a 95% confidence interval at a 0.05 significance level. All statistical analyses were conducted with SPSS version 26 (IBM, USA).

3.4 Results

The participants' sociodemographic characteristics, consisting of 169 (64.8%) women and 92 (35.2%) men, are summarized in Table 3.1. A significant proportion of the participants, 166 (63.6%), were recruited from the rural area. The mean (SD) age of participants was 49.7 (13.6) years, and 54.0% were between 40 and 59 years. Overall, more than 90% of the participants had attended some primary education or higher, and those in the urban area were more likely to have attended secondary school level or higher (57.9%) compared to their rural counterparts (30.7%). Most participants (66.0%) reported that they depended on subsistence or self-employed work, such as fishing and farming. Only five percent of those living in the rural area had salaried employment compared to 22.1% in the urban area. On the other hand, a higher proportion of the urban participants reported that they were not working compared to those from the rural area (23.2% v. 9.6%). A majority of participants (64.5%) from the rural study area reported lower estimated monthly incomes than urban participants (6.3%).

The mean (SD) absolute handgrip strength and relative handgrip strength were 28.8 (7.3) kg and 1.16 (0.40) kg/BMI, respectively. Characteristics of the participants, according to T2DM status, are reported in Table 3.2. Those with prediabetes and T2DM were older *(P*=0.006*)* and more likely to be from the urban area *(P*<0.001*)*. They also had a higher body mass index *(P*<0.001*)*, lower relative handgrip strength *(P*<0.001*),* and were more likely to be classified as having dyslipidemia

(*P*=0.020). No significant differences were observed according to sex, hypertension status, and lifestyle factors such as vigorous physical activity, smoking status, and alcohol consumption.

Men and women differed significantly in terms of mean values of waist circumference (82.8 ± 9.8 vs 88.5 ± 11.2 cm, P < 0.001), total cholesterol (169.1 ± 40.7 vs 181.3 ± 50.4 mg/dL, P < 0.048), and LDL cholesterol (96.7 ± 31.2 vs 108.2 ± 37.5 mg/dL, P =0.012), with men tending to have healthier cardiovascular biomarker values compared to women (Table 3.3). Relative handgrip strength was well correlated with anthropometric and body composition measures such as waist circumference (r=-0.510, P<0.001), hip circumference (r=-0.572, P<0.001), body fat (r=-0.501, P<0.001) muscle mass (r=0.521, P<0.001), and muscle quality (r=0.215, P=0.037). The results are shown in Table 3.4.

Additionally, there was a tendency for higher relative handgrip strength to be associated with lower systolic blood pressure (β [SE]; -4.56 [4.95]; P=0.358), diastolic blood pressure (β [SE]; -4.94 [2.80]; P=0.078), fasting plasma glucose (β [SE]; -1.00 [0.71]; P=0.159), total cholesterol (β [SE]; -0.52 [0.29]; P=0.062), LDL cholesterol (β [SE]; -0.47 [0.22]; P=0.030), triglycerides (β [SE]; -0.35 [0.21]; P=0.088) and higher HDL cholesterol level (β [SE]; 0.05 [0.10]; P=0.657). The models were adjusted by age (continuous), sex, and place of residence (Table 3.5).

The logistic regression analysis results for the association of prediabetes and T2DM with relative handgrip strength are shown in Table 3.6. In the unadjusted model, the odds ratio (OR) of prediabetes and type 2 diabetes mellitus per unit increase of relative handgrip strength was 0.12 [95% CI; 0.04-0.33]. The result remained significant after adjusting for age (continuous), sex, place of study, and hypertension (AOR [95% CI]; 0.16 [0.03-0.75]). The lower odds of prediabetes and type 2 diabetes were still found after further adjustment with dyslipidemia and level of education (AOR [95% CI]; 0.19 [0.03-0.95]).

3.5 Discussion

This cross-sectional study of participants from Malawi's urban and rural areas found that relative handgrip strength is associated with prediabetes and type 2 diabetes mellitus. This simple muscle strength measure was also well correlated with anthropometric and body composition measures among the participants. Additionally, relative handgrip strength was associated with other cardiovascular disease biomarkers. Body mass index alone has a limitation in assessing body composition since it lacks sensitivity for assessing disease risks, especially in people who have normal or mildly elevated BMI [10]. Therefore, handgrip grip strength measurement would provide an opportunity for prediabetes and type 2 diabetes risk screening. Handgrip strength testing is cheap, non-invasive, and is easy to conduct in fieldwork, which would make its adoption in health examinations effortless. Furthermore, like body mass index, participants quickly understood their handgrip strength measurement outcome, which would motivate them to change their lifestyle.

To the best of my knowledge, this is the first study in sub-Saharan Africa to examine the association of relative handgrip strength with prediabetes and T2DM among both rural and urban populations. However, the use of simple binary logistic regression models of handgrip strength for the screening of diabetes was reported earlier in a smaller study in Kenya. The participants of that study were recruited from a diabetic hospital and surrounding locations [20]. Our findings show that relative handgrip strength may have utility in disease screening among a population with wide-ranging sociodemographic characteristics. Most of the study participants from the rural area depended on subsistence work such as farming and fishing. In contrast, most of those from the urban area were self-employed or employed by the government. The occupation was suspected to influence participants' handgrip strength and its subsequent association with prediabetes and T2DM; to the contrary, the present study findings on the association of relative handgrip strength with prediabetes and T2DM are similar to those reported elsewhere [14,21,22].

However, it should be noted that the mean handgrip strength and relative handgrip strength in this population were lower than those reported in earlier studies. Participants recruited in the present study were either prediabetic or prehypertensive during the baseline NCDs survey, which might explain the difference. Furthermore, unlike in the earlier studies, robust adjustment for all distal and proximal risk factors was not done due to the smaller number of participants in the present study. We recommend future population studies to consider these.

Participants from the urban area had a higher proportion of prediabetes and T2DM. This was expected since higher prediabetes and T2DM prevalence was also reported in the urban population in the earlier study [4]. The urban population has higher rates of cardiovascular risk factors such as obesity and physical inactivity (although the levels are still above WHO physical activity recommendations). Indeed, the present study showed that body mass index was associated with prediabetes and T2DM. However, this finding should be interpreted with care. The extensive cross-sectional study from the same population investigating various cardiovascular risk factors found that a substantial proportion of people with diabetes were not overweight or obese (46% of urban and 26% of rural diabetes individuals) [4]. Similar to the previous study findings, alcohol consumption and smoking were not associated with prediabetes and T2DM. This population has a lower prevalence of these lifestyle risk factors.

A few prospective studies suggest that reduced muscle strength and quality may play a role in the development of prediabetes and type 2 diabetes [13,23]. While the underlying mechanism is not well understood, some physiological research suggests a potential causal pathway that points to the benefit of muscle strength and quality. Exercise training, which may improve muscle strength and quality, is reported to favor increased insulin-stimulated glucose uptake in skeletal muscle in contrast to adipose tissues [24]. Besides, previous studies suggest that the role of muscle strength in the development of insulin resistance may be separate from that of skeletal muscle fat content [25]. Handgrip strength measurement may thus provide a way to assess overall muscle strength and quality, which is associated with prediabetes and T2DM risk.

There is evidence that lifestyle interventions conducted among prediabetes individuals may help them revert to normal glucose levels or delay progression to T2DM [26]. This study findings show that relative handgrip strength was not only associated with T2DM but also prediabetes in this population comprising of both urban and rural participants. Therefore, these findings suggest that using relative handgrip strength may help identify individuals at a high risk of prediabetes who can benefit from intervention programs. On the other hand, muscle strength is also associated with a wide range of health conditions, including nutrition [27], mental health [28], and increased mortality [16,29]. Therefore, assessment of handgrip strength may benefit not only for prediabetes and T2DM screening but also during general health examinations. Further studies are required to establish screening cutoff points for prediabetes and T2DM risk in this population.

The present study has some strengths; given the paucity of muscle strength studies and diabetes in the sub-Saharan African population, this study provided some preliminary evidence on adopting handgrip strength measurement in health examinations. Notably, the study participants came from diverse rural and urban populations, enhancing the findings' generalizability.

Some limitations of the study should be noted. Since this study was cross-sectional, causality cannot be reported. Additionally, BMI stratified analyses were not conducted due to the smaller number of participants. However, a previous study from the same population found an increased risk of diabetes at a relatively low or normal body mass index compared to data from high-income countries [4]. Therefore, handgrip strength may help stratify prediabetes and type 2 diabetes risk among this population, as observed in other studies. The smaller number of participants in the study also prevented the construction of models with full adjustment for all distal and proximal factors.

Additionally, this study recruited more women than men. Women were more likely to be found at home during the data collection period. However, this study reports significant findings. It provides important preliminary findings, which could lead to more research on this subject in the region. The study only used fasting plasma glucose when determining prediabetes and T2DM. This may have resulted in the misclassification of individuals with impaired insulin secretion capacity since these individuals may have different characteristics. Furthermore, all lifestyle characteristics were self-reported. However, self-reported lifestyle characteristics are commonly used in type 2 diabetes population studies [30].

Conclusion

This study found that relative handgrip strength is associated with prediabetes and type 2 diabetes among the adult rural and urban populations in Malawi. The findings provide evidence for the adoption of handgrip strength measurement during health examinations in Malawi, which most of the time only include body mass index measurement. Given earlier evidence of a high prevalence of diabetes among normal-weight individuals, handgrip strength measurement may provide an opportunity for prediabetes and type 2 diabetes risk screening in Malawi.

3.6 References

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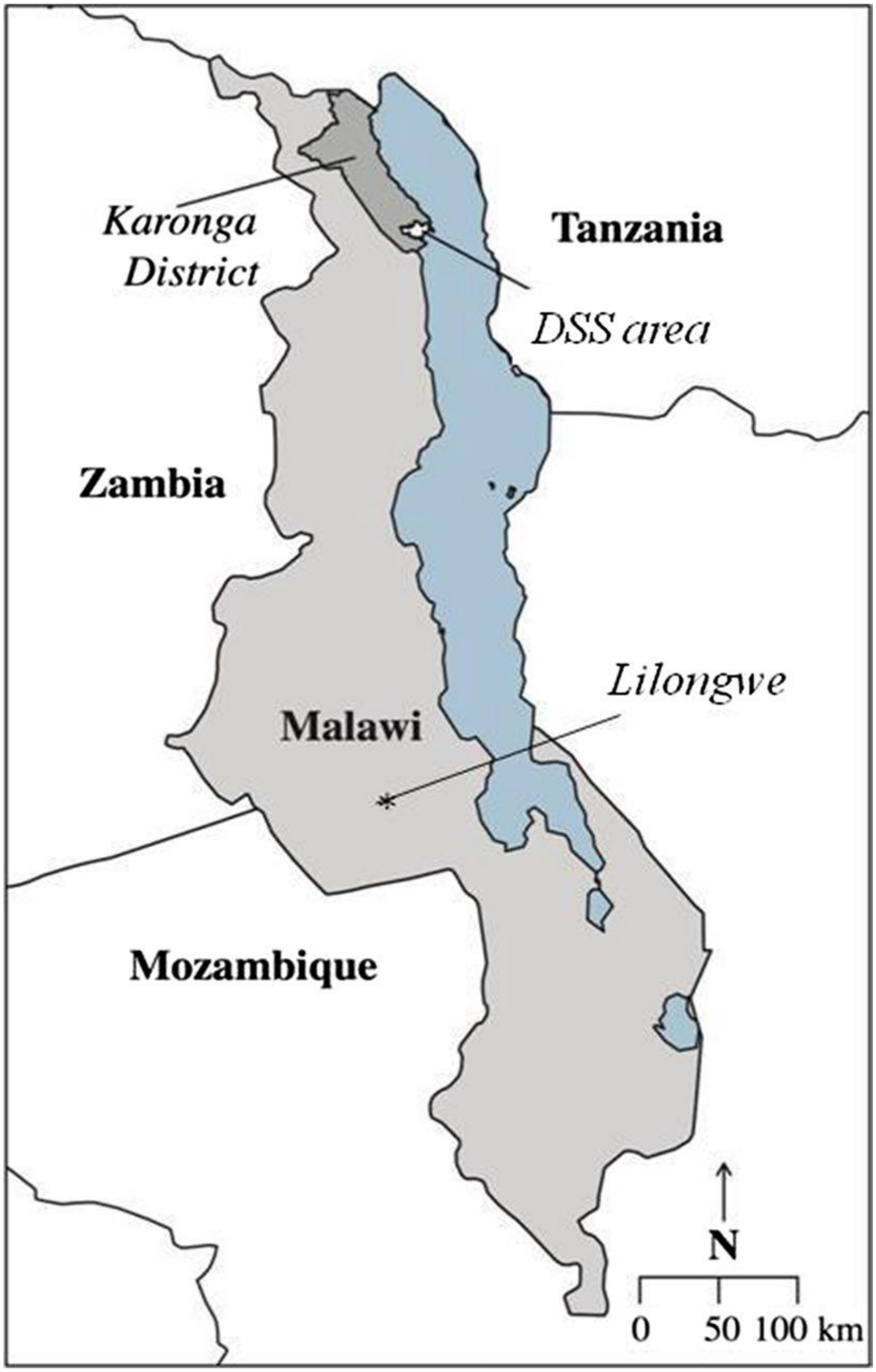

Figure 3.1 Map of Malawi showing locations of the urban and rural study areas.

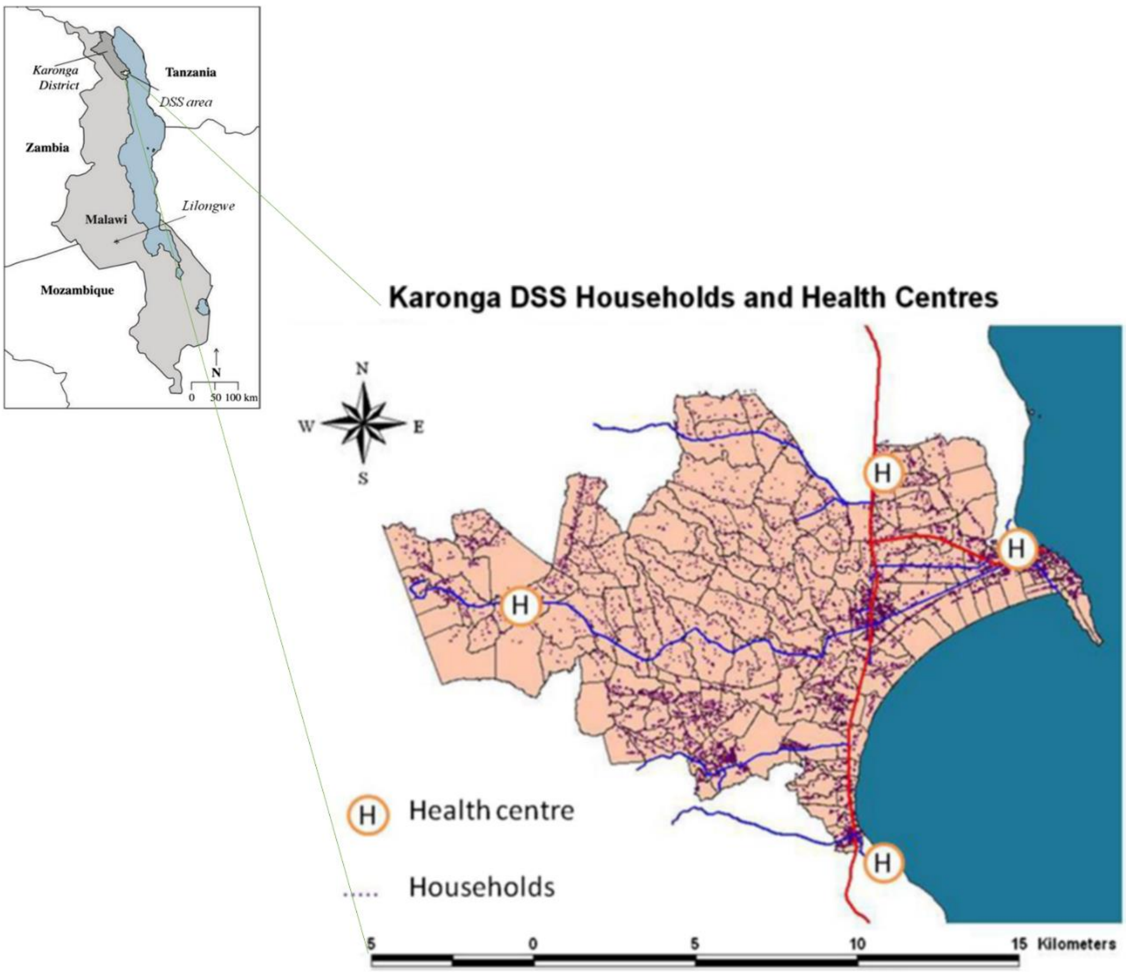

Figure 3.2 Karonga Demographic Surveillance Site (DSS) study area.

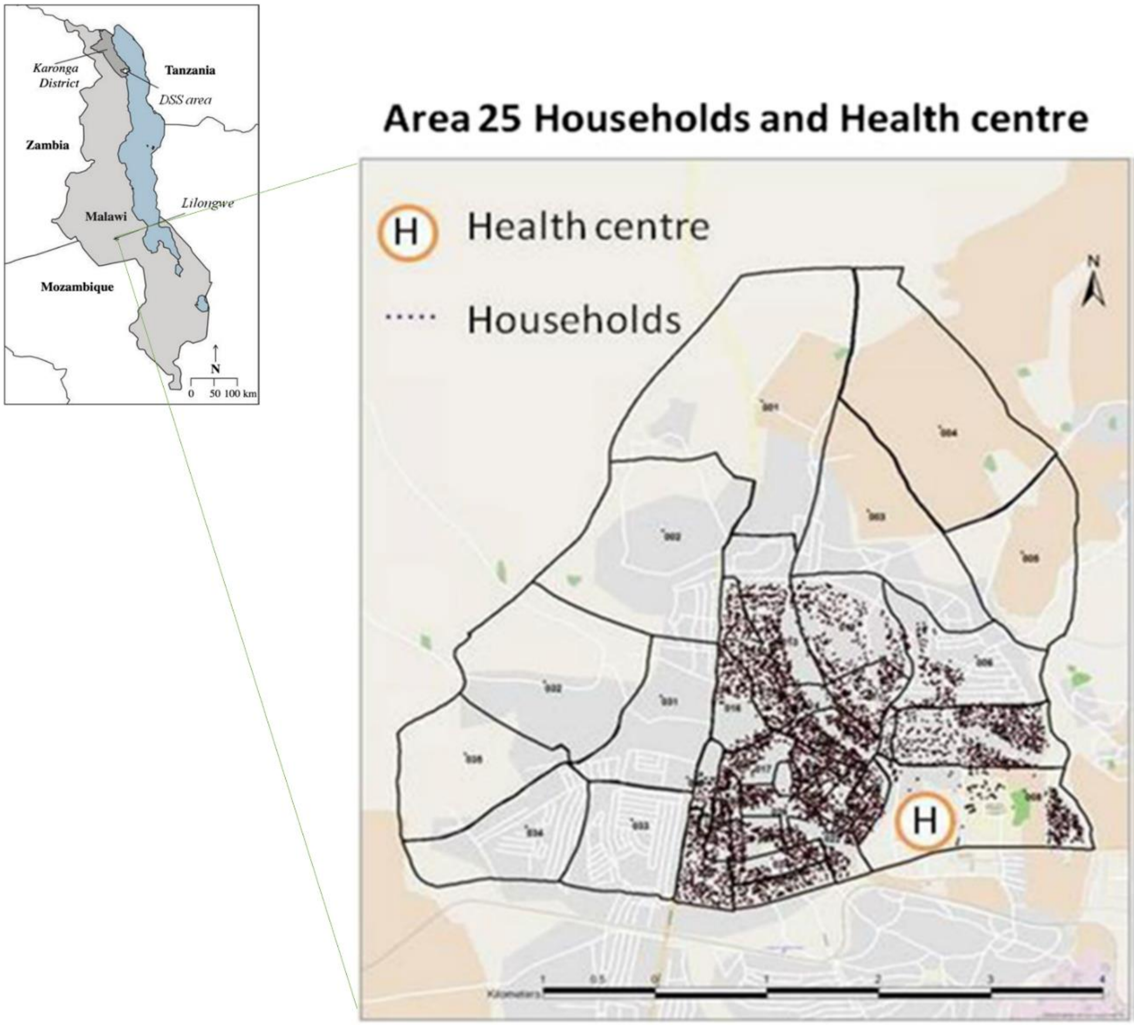

Figure 3.3 Lilongwe (Area 25) study area.

Table 3.1 Sociodemographic characteristics of the study participants according to the place of study.

Characteristic	Total N = 261	Karonga (rural) n = 166 (63.6%)	Lilongwe (urban) n = 95 (36.4%)
Age (years), mean ± SD [a]	49.7 ± 13.6	50.3 ± 13.4	48.8 ± 13.9
Age group (years)			
20 – 39	59 (22.6)	35 (21.1)	24 (25.2)
40 – 59	141 (54.0)	92 (55.4)	49 (51.6)
60+	61 (23.4)	39 (23.5)	22 (23.2)
Sex			
Women	169 (64.8)	100 (60.2)	69 (72.6)
Men	92 (35.2)	66 (39.8)	26 (27.4)
Educational achievement			
None	18 (6.9)	2 (1.2)	16 (16.8)
Primary	137 (52.0)	113 (68.1)	24 (25.3)
Secondary	84 (32.2)	46 (27.7)	38 (40.0)
Post-secondary	22 (8.4)	5 (3.0)	17 (17.9)
Employment			
Not working	38 (14.6)	16 (9.6)	22 (23.2)
Housework	16 (6.1)	11 (6.6)	5 (5.2)
Subsistence	106 (40.6)	103 (62.1)	3 (3.1)
Self-employed	66 (25.3)	28 (16.9)	38 (40.0)
Salaried	29 (11.1)	8 (4.8)	21 (22.1)
Missing	6 (2.3)	0 (0)	6 (6.3)
Monthly family income			
Lower ≤ MWK 20,000 (26 USD)	113 (43.3)	107 (64.5)	6 (6.3)
Middle ≤ MWK 100,000 (USD 131)	83 (31.8)	49 (29.5)	34 (35.8)
Upper MWK>100,000 (USD 131)	54 (20.7)	5 (3.0)	49 (51.6)
Missing	11 (4.2)	5 (3.0)	6 (6.3)

[a]SD: Standard deviation.

Table 3.2 Characteristics of the study participants according to T2DM status.

Characteristic	Normal n = 209 (80.1)	Prediabetes n = 21 (8.0)	T2DM n = 31 (11.9)	*p-value*
Age (years), mean ± SD	48.5 (13.5)	52.4 (12.3)	56.5 (12.8)	0.006
Age group (years)				
20 – 39	53 (25.4)	4 (19.1)	2 (6.5)	0.020
40 – 59	114 (54.5)	12 (57.1)	15 (48.4)	
60+	42 (20.1)	5 (23.8)	14 (45.1)	
Sex				0.126
Women	129 (61.7)	16 (76.2)	24 (77.4)	
Men	80 (38.3)	5 (23.8)	7 (22.6)	
Place of study				< 0.001
Karonga (rural)	146 (69.9)	8 (38.1)	12 (38.7)	
Lilongwe (urban)	63 (30.1)	13 (61.9)	19 (61.3)	
BMI (kg/m^2), mean ± SD	25.1 ± 4.8	29.0 ± 6.8	30.5 ± 5.1	< 0.001
BMI categories				< 0.001
Underweight	6 (2.9)	0 (0.0)	0 (0.0)	
Normal	110 (52.6)	5 (23.8)	5 (16.1)	
Overweight	56 (26.8)	8 (38.1)	9 (29.0)	
Obese	37 (17.7)	8 (38.1)	17 (54.9)	
HGS (kg), mean ± SD	29.2 ± 7.5	27.4 ± 6.9	26.6 ± 6.0	0.119
RHGS (kg/BMI), mean ± SD	1.21 ± 0.4	1.0 ± 0.1	0.9 ± 0.3	< 0.001
Hypertension				0.129
No	109 (52.2)	8 (38.1)	11 (35.5)	
Yes	100 (47.8)	13 (61.9)	20 (64.5)	
Dyslipidemia				0.020
No	95 (46.1)	6 (28.6)	6 (21.4)	
Yes	111 (53.9)	15 (71.4)	22 (78.6)	
Vigorous physical activity [a]				0.553
No	137 (67.2)	11 (55.0)	20 (64.5)	
Yes	67 (32.8)	9 (45.0)	11 (35.5)	
Smoking [a]				0.101
Not current	187 (78.6)	20 (100.0)	31 (100.0)	
Current	17 (8.3)	0 (0.0)	0 (0.0)	
Alcohol consumption [a]				0.296
Not in last year	136 (66.7)	14 (70.0)	25 80.6)	
In last year	68 (33.3)	6 (30.0)	6 (19.4)	

Abbreviations: T2DM: Type 2 diabetes mellitus; SD: Standard deviation; BMI: body mass index; HGS: handgrip strength; RHGS: relative handgrip strength. [a] Number of participants with information = 255.

Table 3.3 Participants biomarker values by sex.

Characteristic		**Men** n = 92	**Women** n = 169	***P*-value** [b]
Waist circumference	cm	82.8 ± 9.8	88.5 ± 11.2	< 0.001
Systolic blood pressure	mmHg	130.6 ± 16.7	134.6 ± 22.2	0.126
Diastolic blood pressure	mmHg	83.0 ± 10.7	85.0 ± 11.4	0.159
Total cholesterol	mg/dL	169.1 ± 40.7	181.3 ± 50.4	0.048
HDL cholesterol	mg/dL	47.5 ± 16.4	46.4 ± 15.5	0.596
LDL cholesterol	mg/dL	96.7 ± 31.2	108.2 ± 37.5	0.012
Triglycerides [a]	mg/dL	111.2 (79.3 – 158.5)	96.1 (65.1 – 157.9)	0.254
Relative handgrip strength	kg/BMI	1.5 ± 0.3	0.9 ± 0.2	< 0.001

Abbreviations: HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Means and standard deviations are shown for continuous variables and the number of participants and percentages for categorical variables.

[a]Data for triglycerides were skewed and therefore are presented as median (interquartile range) values and P-values obtained with the Kruskal-Wallis test.

[b]P-values were obtained with the t-test.

Table 3.4 Correlation of relative handgrip strength and body composition measures.

		Waist Circumf.	Hip Circumf.	Waist to Hip ratio	Body fat	Muscle quality	Muscle mass	Relative hand grip strength
Waist Circumf.	Pearson Correlation	1	.811**	.620**	.484**	-.061	.115	-.510**
	Sig. (2-tailed)		.000	.000	.000	.571	.285	.000
	N	250	250	250	88	88	88	250
Hip Circumf.	Pearson Correlation	.811**	1	.048	.547**	-.134	-.070	-.572**
	Sig. (2-tailed)	.000		.448	.000	.211	.517	.000
	N	250	255	250	89	89	89	255
Waist to Hip ratio	Pearson Correlation	.620**	.048	1	.075	.067	.272*	-.112
	Sig. (2-tailed)	.000	.448		.488	.536	.010	.076
	N	250	250	250	88	88	88	250
Body fat	Pearson Correlation	.484**	.547**	.075	1	.605**	.267**	-.501**
	Sig. (2-tailed)	.000	.000	.488		.000	.009	.000
	N	88	89	88	95	95	95	95
Muscle quality	Pearson Correlation	-.061	-.134	.067	.605**	1	.758**	.215*
	Sig. (2-tailed)	.571	.211	.536	.000		.000	.037
	N	88	89	88	95	95	95	95
Muscle mass	Pearson Correlation	.115	-.070	.272*	.267**	.758**	1	.521**
	Sig. (2-tailed)	.285	.517	.010	.009	.000		.000
	N	88	89	88	95	95	95	95
Relative handgrip strength	Pearson Correlation	-.510**	-.572**	-.112	-.501**	.215*	.521**	1
	Sig. (2-tailed)	.000	.000	.076	.000	.037	.000	
	N	250	255	250	95	95	95	261

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 3.5 Results of multiple linear regression of relative handgrip strength on selected biomarker outcomes.

Characteristic		***β***	**SE**	***p-value***
Systolic blood pressure	(mmHG)	-4.56	4.95	0.358
Diastolic blood pressure	(mmHG)	-4.94	2.80	0.078
Fasting plasma glucose	(mmol/L)	-1.00	0.71	0.159
Total cholesterol	(mmol/L)	-0.52	0.29	0.062
HDL cholesterol	(mmol/L)	0.05	0.10	0.657
LDL cholesterol	(mmol/L)	-0.47	0.22	0.030
Triglycerides	(mmol/L)	-0.35	0.21	0.088

Abbreviation: SE: standard error; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

All models adjusted for age (continuous), sex, and place of residence.

Table 3.6 Unadjusted and adjusted association of prediabetes and type 2 diabetes with relative handgrip strength.

		OR/aOR	95% CI	
			Lower	Upper
N	254			
Cases (%)	50 (19.7)			
Unadjusted model	OR,	0.12	0.04	0.33
Model 1	aOR,	0.16	0.03	0.70
Model 2	aOR,	0.16	0.03	0.75
Model 3	aOR,	0.19	0.03	0.95

Abbreviation: OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

Model 1: adjusted for age (continuous), sex, and place of study.

Model 2: adjusted for age (continuous), sex, and place of study, and hypertension.

Model 3: adjusted for age (continuous), sex, place of study, hypertension, dyslipidemia, and level of education.

Chapter 4: Overall discussion and conclusion

The present study provides evidence that reduction of muscle strength precedes the development of prediabetes among adults. In the first study, I found that baseline relative handgrip strength predicts incident prediabetes among adults in Japan. Similarly, the second study also found that relative handgrip strength was associated with prediabetes and type 2 diabetes mellitus among urban and rural-dwelling adults in Malawi. The most important finding was that this relationship was significant among normal-weight individuals. A substantial proportion of type 2 diabetes mellitus cases in Japan and Malawi are normal or slightly overweight. The results suggest that handgrip strength measurement is useful to identify individuals at high risk of prediabetes, importantly, among normal-weight individuals. The identified individuals may benefit from early intervention to reduce the risk of prediabetes and cardiovascular diseases.

A few studies have reported the association of handgrip strength [1,2] and relative handgrip strength [3] with incident type 2 diabetes mellitus. However, this is the first study to report the longitudinal relationship of relative handgrip strength with incident prediabetes among adults. Individuals with prediabetes, defined as impaired fasting glucose or raised hemoglobin A1c have a high risk of composite cardiovascular events, coronary heart diseases, stroke, and all-cause mortality [4]. Moreover, early intervention in prediabetes individuals significantly reduced the progression rate to overt type 2 diabetes mellitus, with some reverting to normal blood glucose levels [5]. Therefore, findings in this study have unique implications on the early implementation of preventive programs by providing evidence that handgrip strength measurement may help identify individuals at higher risk of incident prediabetes.

The Malawi study was the first to characterize handgrip strength and report their relationship with prediabetes and type 2 diabetes in a sub-Saharan Africa population. The study provided preliminary evidence on the use of handgrip strength in non-communicable disease risk screening in sub-Saharan Africa. There are still questions about overweight and obesity's contribution to the variance of the prevalence of non-communicable diseases in sub-Saharan Africa. These questions arise from the finding that a substantial number of those with type 2 diabetes mellitus tend to have normal or slightly elevated body mass index [6]. Therefore, results from western populations that have long been extrapolated to other populations such as those in sub-Saharan Africa and Asia may not be entirely consistent with research findings from these settings [7]. Our study on muscle strength and quality among adults in a sub-Saharan African population provides evidence of additional risk factors to consider in NCDs control. Our work is useful in implementing and monitoring NCDs preventive programs, especially in settings with significantly different risk factors than those reported elsewhere.

In conclusion, this study's findings lead to two crucial recommendations on the application of handgrip strength. First, muscle strength measurement may be used to identify individuals at risk of prediabetes. These individuals may be motivated to change their lifestyle. Through my experience during handgrip strength testing, participants were interested in knowing the meaning of their results and were quick to ask for examples of interventions they could apply to improve their muscle strength. Currently, resistance training exercises, including simple elastic resistance training that can be performed at home, are reported to improve muscle strength and functional performance [8,9]. In extension, handgrip strength may also be useful to monitor the progress of exercise and muscle strengthening intervention programs in the communities. However, I noted that there are no handgrip strength cut-off points for type 2 diabetes mellitus and NCDs risk. Some studied have published normal handgrip strength reference values for healthy adults [10]. However, there is a need for research to derive simple cut-off points for relative handgrip strength to identify those at increased risk of prediabetes and type 2 diabetes mellitus. This would accelerate the adoption of handgrip strength into medical examinations.

Second, muscle strength may be uniquely necessary for stratifying prediabetes and type 2 diabetes risk among normal-weight adults. Measurement of body mass index is popular; in most cases, it is the only one considered during medical examinations. There is evidence that body mass index has a limitation in assessing body composition, especially among those with normal or slightly elevated body weight [11]. Therefore, our results highlight the need to use different risk indicators while screening for type 2 diabetes mellitus risk. There is merit in including handgrip strength measurement in routine medical examinations considering the limitations of body mass index.

Moreover, handgrip strength measurement is cheap, quick, and well correlated with overall muscle strength and other body composition measures. Additionally, muscle strength measurement utility goes beyond prediabetes and type 2 diabetes mellitus screening since it has been associated with various health states, including all-cause mortality [12–14]. Therefore, this study recommends including handgrip strength measurement in medical examinations.

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Appendices

Appendix 1.0 Collinearity statistics of exposure variable and variables of interest in the models of new prediabetes cases with increasing relative handgrip strength (all participants).

	Collinearity Statistics					
	Model 1		Model 2		Model 3	
	Tolerance	**VIF**	**Tolerance**	**VIF**	**Tolerance**	**VIF**
Age	0.976	1.024	0.854	1.171	0.853	1.172
Sex	0.452	2.212	0.399	2.504	0.399	2.508
Relative handgrip strength	0.446	2.241	0.417	2.397	0.416	2.403
Dyslipidemia			0.882	1.134	0.881	1.136
Hypertension			0.844	1.184	0.841	1.188
Smoking status			0.920	1.087	0.919	1.088
Alcohol consumption frequency			0.902	1.109	0.899	1.112
Regular physical activity					0.979	1.022

Dependent variable: New prediabetes cases

Abbreviations; VIF: Variance Inflation Factor

Appendix 2.0 Biomarker values by sex at baseline stratified by age.

Characteristic		Age≤50 years			Age >50 years		
		Men n = 444	Women n = 313	*P*-value [b]	Men n = 149	Women n = 169	*P*-value [b]
Waist circumference	cm	83.5 ± 9.5	76.2 ± 9.8	< 0.001	83.7 ± 6.8	79.4 ± 10.1	< 0.001
Systolic blood pressure	mmHg	127.4 ± 15.0	117.0 ± 12.9	< 0.001	134.9 ± 18.6	130.3 ± 22.6	0.049
Diastolic blood pressure	mmHg	77.7 ± 11.5	71.2 ± 11.4	< 0.001	84.6 ± 12.4	76.7 ± 13.7	< 0.001
Total cholesterol	mg/dL	192.7 ± 33.4	188.8 ± 33.3	0.114	203.0 ± 29.8	217.2 ± 33.8	< 0.001
HDL cholesterol	mg/dL	55.1 ± 13.2	66.4 ± 14.3	< 0.001	57.3 ± 14.4	68.8 ± 16.3	< 0.001
LDL cholesterol	mg/dL	117.9 ± 31.2	106.7 ± 27.6	< 0.001	124.0 ± 29.6	128.2 ± 29.1	0.200
Triglycerides [a]	mg/dL	70.0 (53.0 – 102.0)	57.0 (47.0 – 80.0)	< 0.001	91.0 (64.0 – 128.0)	67.0 (44.7 – 74.0)	< 0.001
Creatinine	mg/dL	0.9 ± 0.1	0.6 ± 0.1	< 0.001	0.9 ± 0.1	0.6 ± 0.1	< 0.001
Relative handgrip strength	kg/BMI	1.7 ± 0.3	1.1 ± 0.2	< 0.001	1.7 ± 0.3	1.1 ± 0.2	< 0.001

Abbreviations: HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Means and standard deviations are shown for continuous variables and the number of participants and percentages for categorical variables.

[a]Data for triglycerides were skewed and therefore are presented as median (interquartile range) values and P-values obtained with the Kruskal-Wallis test.

[b]P-values were obtained with the t-test.

Appendix 3.0 Collinearity statistics of exposure variable and variables of interest in the models of prediabetes and type 2 diabetes mellitus cases with increasing relative handgrip strength.

	Collinearity Statistics					
	Model 1		Model 2		Model 3	
	Tolerance	VIF	Tolerance	VIF	Tolerance	VIF
Age	0.794	1.259	0.776	1.289	0.739	1.353
Sex	0.448	2.235	0.447	2.235	0.431	2.320
Relative handgrip strength	0.373	2.684	0.364	2.748	0.352	2.838
Study place	0.900	1.111	0.898	1.114	0.813	1.229
Hypertension			0.874	1.144	0.862	1.160
Dyslipidemia					0.949	1.054
Level of education					0.793	1.261

Dependent variable: Prediabetes and type 2 diabetes mellitus cases
Abbreviations; VIF: Variance Inflation Factor

Source

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