EXPLORING THE RELATIONSHIP BETWEEN PARITY AND CARDIOVASCULAR RISK IN OLDER FEMALES WITH MILD COGNITIVE IMPAIRMENT

by

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Abstract

As the population of older adults is expected to rise exponentially, the necessity for a clearer understanding of the components that contribute to age-related changes in cognitive function cannot be overstated. It is critical to understand the risk factors for cognitive decline and dementia in order to improve early detection and prevention. Females are disproportionately affected by Alzheimer's Disease and other dementias due to contributing factors such as age and sex hormones. Pregnancy is a significant hormonal event in a female's life and has been found to be associated with increased cardiovascular risk. While the relationship between pregnancy and cardiovascular risk in later life is well-established, whether the number of pregnancies influences this risk still requires further exploration. In this cross-sectional study, the differences in cardiovascular risk as well as executive function among levels of parity in older females with mild cognitive impairment were assessed. Further, the influence physical fitness has on the relationships between parity and cardiovascular risk as well as parity and executive function in older females with mild cognitive impairment was explored. Baseline data were compiled from two ongoing randomized controlled trials within the Aging, Mobility, and Cognitive Health Lab. Results showed that cardiovascular risk was lowest among primiparous females compared with multiparous females and yet, executive function was lowest among primiparous females and highest among females having given birth twice. In addition, physical fitness did not moderate the relationship between cardiovascular risk and parity nor did it moderate the relationship between parity and executive function. The findings from this highlight the importance of taking reproductive health into consideration when evaluating cardiovascular and cognitive health in females in later life.

Lay Summary

Alzheimer's Disease and other dementias are the leading cause of death in females in Canada. Cardiovascular disease risk factors are predominant contributors to the development of dementia. Given that low levels of cardiovascular risk have been found to be associated with preservation of cognitive function in older females, sex-specific life events such as childbearing must be considered when discussing cardiovascular and cognitive health in females. This thesis showed differences in cardiovascular risk as well as executive function as a function of parity in older females with mild cognitive impairment. Cardiovascular risk was lowest among primiparous females compared with multiparous females and yet, executive function was lowest among primiparous females and highest among females having given birth twice. These findings provide greater insight into the long-term impact childbearing has in influencing both cardiovascular and cognitive health in females in later life.

Preface

This dissertation was written and compiled by Madison Welch. All of the work presented henceforth was conducted in the Aging, Mobility, and Cognitive Health Laboratory at the University of British Columbia, Vancouver. All projects and associated methods were approved by the University of British Columbia's Research Ethics Board [certificates #H15-02181 and #H15-00972]. None of the text of the dissertation is taken directly from previously published or collaborative articles.

I was responsible for all major areas of concept formation, data collection and analysis, as well as the majority of manuscript composition. Drs. Teresa Liu-Ambrose, Cindy Barha, and Liisa Galea were involved in concept formation and manuscript edits. Research assistants and graduate students within the Aging, Mobility, and Cognitive Health Laboratory were responsible for data collection. Teresa Liu-Ambrose was the supervisory author on this project and was involved throughout the project in concept formation and manuscript edits.

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1. BACKGROUND

1.1 Introduction

A wide range of physiological and cognitive changes occur with age (1,2). As the population of older adults is expected to rise exponentially, the necessity for a clearer understanding of the factors that contribute to these changes cannot be overstated. With aging, performance declines in multiple cognitive domains, including memory, attention, and executive functions (3). For some, this decline is a product of normal ageing, while for others these reductions in cognitive function become more severe resulting in interference with activities of daily living (i.e., dementia) (4). Dementia is a global health epidemic with over 50 million cases worldwide in 2020 (5). Each year, there are over 9.9 million new cases of dementia worldwide with the expectation of reaching 152 million cases by 2050 (5). It is therefore critical to understand the modifiable risk factors for cognitive decline and dementia in order to improve early detection and prevention.

Females[1] comprise approximately two-thirds of Canadians with Alzheimer's Disease (AD) and dementia (6), highlighting the increased risk of developing dementia, compared with males. Annually, there are approximately 76,000 new cases of dementia diagnosed in Canada (2017) with 15.8 new cases per 1,000 seniors being females (6). Further, AD and other dementias are the leading cause of death in females in Canada (7). While reasons for this sex

[1] **Sex** refers to a set of biological attributes that is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorized as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed. (188)
Gender refers to the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people. Gender is usually conceptualized as a binary (girl/woman and boy/man) yet there is considerable diversity in how individuals and groups understand, experience, and express it. (188)

difference remain unclear, females living longer than males may be a contributing factor as age is the greatest risk factor for developing AD (8). Further, sex differences in AD risk may depend on the geographical region as educational access and attainment for females may vary across countries (9).

Vascular dementia (VD) is the second most common form of dementia and is caused by impairment of blood flow to the brain resulting in cognitive impairment (10). Vascular cognitive impairment (VCI) is characterized by cognitive decline as a result of vascular damage and affects cognitive domains such as memory, problem solving, and executive function (11,12). VCI has also been found to have a synergistic effect with AD whereby both conditions contribute to worsening cognitive decline (11,13). As VCI and cardiovascular disease (CVD) share predominant risk factors (11), it is important to consider the impact CVD and its risk factors have on cognition and how the risk may differ among sexes.

Mild cognitive impairment (MCI) is defined as cognitive decline greater than what is expected for an individual's age and education level but does not interfere with activities of daily living (14). MCI can be considered a risk state for dementia as more than half of individuals with MCI progress to dementia (14). CVD risk factors have been found to contribute to an increased risk of developing MCI as well as dementia (15,16). Although older adults with MCI are at an increased risk of developing dementia, not all of those considered to have MCI will progress to dementia. Therefore, MCI is a critical stage to intervene and prevent progression or delay the onset of dementia by identifying the contributing risk factors.

1.2 Cardiovascular Disease & Cognitive Health

Cardiovascular disease risk factors are predominant contributors to the development of MCI, VCI, and other dementias (11,16). CVD is a term used when referring to all types of diseases that affect the heart or blood vessels and include conditions such as coronary heart disease, stroke, and peripheral artery disease (17). CVD is the leading cause of death globally for both males and females and is responsible for 32% of all global deaths (18). While incidence of CVD is higher among males, females have a higher rate of CVD-related mortality (19). Shared risk factors such as hypertension, diabetes, smoking, and obesity are associated with an increased risk of developing both CVD and VCI (11). Further, risk factors such as midlife hypertension and total cholesterol are associated with the development of MCI in later life (15,16). If these conditions are left untreated, MCI can progress in severity and put the individual at risk of developing VCI (15). There are numerous mechanisms that aim to explain the influence these risk factors have on VCI risk. As the vascular system is responsible for supplying blood to the brain, conditions such as hypertension or diabetes have the potential to impair cerebral perfusion (20,21). Hypoperfusion of the brain promotes the accumulation of amyloid-beta, peptides that contribute to the development of AD by forming plaques within the brain (22). This is a critical component of AD pathogenesis (22) and has been found to lead to neurodegeneration (23). In addition, obesity and high blood pressure, both risk factors of CVD, have shown to promote arterial stiffening (24,25). With greater arterial stiffness, the blood must overcome greater resistance, causing the increased pulse pressure to travel deeper into the periphery, resulting in vascular damage (26). Additionally, due to increased arterial resistance, blood clots can form and cause arteries within the brain to become occluded (11). When this occurs in the smaller vessels of the brain it causes damage to the subcortical areas of the brain, resulting in decreased motor

performance, decreased attention, slower cognitive processing, and executive dysfunction (11). Reduced executive function caused by these structural and functional changes in the brain results in impaired set shifting and working memory (21,27). Understanding the contributing risk factors and how these differ by sex will provide critical information regarding the management and prevention of VCI and AD.

1.3 Sex Differences among Cardiovascular Risk Factors

While CVD mortality rates are typically said to be higher in males than females, the absolute number of CVD deaths among females exceeds that of males (28). This is hypothesized to be a result of females having a longer life expectancy than males as the risk of CVD is greatest in older age (28). Because CVD is the leading cause of death in females worldwide (29), understanding not only age, but other contributing risk factors for CVD such as diabetes, hypertension, smoking, and obesity are also important in considering the level of risk posed to females in particular.

1.3.1 Sex Differences in Diabetes

Diabetes is a disease characterized by elevated blood glucose levels as a result of the body's inability to produce enough insulin or use insulin appropriately (30). Insulin resistance and/or reduced insulin secretion can cause functional and structural alterations in blood vessel walls leading to vascular damage and dysfunction (31). Although the prevalence of diabetes is higher among males than in females (8.4% vs. 6.3%, respectively, in Canada), the risk of developing CVD is much higher for females with diabetes in comparison with males with diabetes (32,33). In a study by Peters et al. (34) comparing diabetics and non-diabetics, it was

found that the risk of developing coronary heart disease (CHD) was 44% greater in females with diabetes compared with males with diabetes. Additionally, it was found that females with diabetes have a significantly higher risk of stroke compared to males with diabetes, even when baseline differences in other CVD risk factors were taken into account (35). Given this increased risk of other cardiovascular related events occurring for females with diabetes, it is important to consider the factors that contribute to these sex differences.

1.3.2 Sex Differences in Hypertension

Hypertension, defined as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg and/or use of antihypertensive medication (36), is a critical factor in determining a person's cardiovascular risk. Health conditions, such as obesity and diabetes increase the risk of developing hypertension (37). While hypertension is more common among males in younger years (< 65 years of age), the inverse is observed in later life (> 65 years of age) whereby it is more common for females (29). Notably, this sex difference in prevalence continues to increase with age; specifically, a 15% and 9% increase is observed for females and males, respectively, when comparing ages 65-74 and 75+ years (29). Reduced hypertension control significantly increases one's risk of a cardiovascular event (38). Males experience reduced hypertension control earlier in life (18-49 years of age) and females later in life (65+ years of age) compared to age-matched peers (38). While there are a number of biological explanations for these observations, the activation of the renin-angiotensin system (RAS) due to a reduction in estrogens in postmenopausal females is likely a primary contributor (39–41). This decrease in endogenous estrogens reduces vasodilation, causing an increase in systolic blood pressure

(29,41). With this increased blood pressure, there is an increased likelihood of developing conditions such as left ventricular hypertrophy, heart failure, and stroke (41).

1.3.3 Sex Differences in Smoking

Smoking is the leading cause of preventable death worldwide (42). While the prevalence of smoking is higher in males compared with females, the risk of coronary heart disease for those who smoke is 25% greater in females compared with males (43), with females experiencing a greater risk of dying from coronary heart disease as well (42). Smoking is considered more detrimental to cardiovascular health in females compared to males as the risk of experiencing an acute myocardial infarction is higher even after adjusting for other cardiovascular risk factors (41,44). Additionally, females who smoked experienced their first acute myocardial infarction 13.7 years earlier when compared to females who did not smoke, versus 6.2 years earlier when comparing smoking and non-smoking males (44). While it is widely accepted that smoking significantly increases cardiovascular risk in females, the specific mechanisms remain unclear (43–45). Some have suggested that tobacco smoke may be responsible for a downregulation of estrogens in premenopausal females (46,47), resulting in greater arterial stiffening and endothelial dysfunction compared to non-smoking females (45), while others have suggested that cigarette smoking is associated with severe coronary lesions forming in the arteries leading to an increased risk of atherosclerosis (46). In postmenopausal females, this antiestrogenic effect caused by smoking may be more detrimental compared with premenopausal females due to the lack of natural estrogen protection that occurs before menopause (46).

1.3.4 Sex Differences in Obesity

According to the World Health Organization (WHO), 39% of the world's adult population are classified as overweight (BMI of 25 - 29.9), while 13% of adults are classified as obese (BMI ≥ 30) (48). While the prevalence of obesity among males and females varies substantially between countries, overall, the proportion of obese females is greater than males (49) whereby females comprise a greater proportion of those who are overweight (40% and 39%, respectively) and a greater proportion of those who are obese compared with males (15% and 11%, respectively) (48). High body mass index (BMI) is one of the most important cardiometabolic risk factors due its contribution to the development of other risk factors such as diabetes, hypertension, and elevated cholesterol (50,51). Visceral and subcutaneous fat are two common ways fat is stored in the body (52), with visceral fat occurring more frequently in males compared with females (52). However, when comparing premenopausal and postmenopausal females, postmenopausal females had significantly greater visceral fat mass as a result of decreased levels of estrogens (52,53). As visceral fat is considered more strongly associated with increased cardiometabolic risk compared to subcutaneous fat (51), it is important to consider the implications of females having higher levels of visceral fat in later life.

Due to a drop in concentration of estrogens during menopause (52,54), females experience a period of elevated susceptibility to weight gain, particularly in the abdominal region (54). The body becomes more resistant to insulin when there is a reduction in levels of estrogens, therefore, decreasing the body's ability to metabolize glucose and lipids (39). Insulin resistance is associated with greater cardiovascular risk in females compared with males (39).

1.3.5 Sex Differences in Arterial Stiffness

Arterial stiffness is one of the best independent predictors of cardiovascular morbidity and mortality (55–57). Stiffness occurs through a number of contributing risk factors such as obesity, hypertension, and age (24).

Obesity can lead to increased insulin resistance, higher levels of leptin production, and increased levels of inflammatory cytokines (52,58), which can influence endothelial and vascular function considerably, leading to increased vascular stiffness (59)(60). High blood pressure has an inverse relationship with arterial stiffness; high blood pressure can promote arterial stiffening (24), while arterial stiffness can accelerate blood pressure progression through an increase in pulse pressure (61). Elevated pulse pressure can then lead to increased aortic wall stress, further contributing to arterial stiffening (61). With age, arterial walls thicken and lose elasticity causing increased arterial stiffness (2,62). Both arterial proinflammation and arterial remodeling occur naturally with age (63). Nitric oxide (NO) and endothelin-1 released by endothelial cells within the walls of the arteries are responsible for the promotion of vascular smooth muscle tone and vasodilation/vasoconstriction (62,63). With age, a reduction in NO bioavailability occurs due to an increase in oxidative stress and a decrease in production by the endothelial cells of the arterial walls (63). As a result, vasodilation is reduced and arteries become stiffer.

These mechanisms collectively contribute to arterial proinflammation and arterial remodeling, contributing to increased arterial stiffness (64). The vascular system must then overcome the increased resistance created by the stiffened arteries, resulting in elevated systolic blood pressure (65). Increased systolic blood pressure then causes elevated ventricular afterload and a decrease in diastolic blood pressure (65,66). As a result, coronary perfusion is reduced (65), therefore, increasing the risk of experiencing a cardiovascular event. Over time, increased

stiffness can lead to left ventricular hypertrophy and heart failure, further increasing the risk of experiencing a cardiovascular event (64).

In healthy young males and females, females have lower baseline arterial stiffness compared with males (55). With age, vascular stiffening increases linearly for both males and females (67); however, a disproportionate increase in stiffening has been observed in females compared to age-matched males – specifically during perimenopause and after menopause (24,68).

The primary mechanism for this sex difference lies in the fluctuation of female sex steroids throughout a female's life and its ability to modulate arterial stiffness (24). Specifically, periods of life when sex steroids are low, such as prepuberty and postmenopause, arteries are stiffer than age-matched males (24,69). Within the cardiovascular system, estrogens promote vascular smooth muscle relaxation via an increase in NO bioavailability, resulting in vasodilatory effects (70). Therefore, with a reduction in levels of estrogens in postmenopausal females, vasodilation decreases (70), contributing to increased systolic blood pressure and arterial stiffness (65). Similarly, males experience increased stiffness before puberty when testosterone levels are lower as the male sex hormone serves as a protective mechanism against vascular stiffening (24).

Arterial stiffness is measured using pulse wave velocity (PWV). PWV measures the rate that blood flows through the circulatory system, specifically the carotid and femoral arteries (71). The velocity of the pressure wave is inversely related to the arterial compliance (71), therefore, a greater PWV value suggests greater arterial stiffness, indicating greater cardiovascular risk.

1.4 Pregnancy & Cardiovascular Disease

Pregnancy is a sex-specific life event that is important to consider when discussing CVD health risk due to its effect on both short and long-term health (72–74). During pregnancy, a female's body undergoes numerous physiological changes in order to ensure healthy development of the growing fetus (73,75,76). The maternal cardiovascular system begins to adapt shortly after conception (77) in order to accommodate the increasing metabolic demands of the fetus (73,77). Large increases in blood volume and cardiac output, as well as reductions in arterial stiffness and blood pressure allow for improved blood flow to the uterus and adequate delivery of oxygen and nutrients to the developing fetus (74,78). Further, increased susceptibility to oxidative stress, increased cholesterol and lipid levels, and increased inflammation within the body occurs within uncomplicated pregnancies (79). Although many of the hemodynamic changes that occur during pregnancy are reversed postpartum (74), there is evidence that suggests some changes remain long-term (80). Due to the changes in heart rate and blood pressure during pregnancy, increases in left ventricular mass and reductions in left ventricular ejection fraction have been found to last into later life (80). As a result of these structural changes, oxygen demand for the heart and arterial pressure increase, putting the mother at greater risk of sudden death compared with those without increased left ventricular mass (81). The presence of risk factors such as increased oxidative stress and elevated lipid levels puts the mother at greater risk of developing CVD later in life (79). Further, CVD risk increases when uncomplicated pregnancies are accompanied by high maternal BMI (79,82).

Conditions such as hypertension, diabetes, and obesity that occur during pregnancy can affect females' health during and following pregnancy (83–85). Some degree of insulin resistance occurs in most pregnancies due to natural weight gain, however, if severe enough, it

can lead to gestational diabetes mellitus – affecting approximately 2-10% of pregnancies in the United States (86). In uncomplicated pregnancies, blood sugar levels typically return to normal shortly following birth; however, females with gestational diabetes are at least seven times more likely to develop type II diabetes in the future (41,87). While weight gain during pregnancy is natural and necessary for fetal development, excessive gestational weight gain has been found to significantly influence maternal health long-term (83,88) whereby those who experienced excessive weight gain were at a greater risk of being overweight and obese 21 years later even after controlling for confounding factors (88). Females that experienced gestational hypertension were found to have a greater prevalence of chronic hypertension and premature CVD later in life when compared to females with normotensive pregnancies (41,84).

While the association between pregnancy and cardiovascular risk in later life is well-established among both complicated and uncomplicated pregnancies, whether the number of pregnancies influences this risk still requires further exploration.

1.5 Parity & Cardiovascular Risk

1.5.1 Physiological/Biological Factors

There are a variety of proposed mechanisms for an increase in cardiovascular risk with parity (number of births). Some research suggests conditions such as diabetes, weight gain, hypertension, or atherosclerosis may contribute to increased cardiovascular risk associated with parity (89–91), while other research indicates it may be due to hormonal or socioeconomical factors (89,92).

Some studies have suggested a link between grand multiparity (≥ 5 live births) and increased risk of developing diabetes (90,93), however, no such association was found at lower

levels of parity (85). In contrast, other findings have demonstrated no increased risk (94) and concluded that it was higher BMI and weight gain, rather than parity, that determined diabetes risk (85,95).

Previous studies examining the association between hypertension and parity have come to conflicting conclusions. Some studies have found the prevalence of hypertension to be associated with higher parity (96), while others have found this association does not exist (97). Regarding both gestational diabetes and hypertension, research has shown that the risk of developing diabetes or hypertension later in life becomes greater if the person has experienced the condition during their pregnancy (84,98).

A longitudinal study by Zoet et al. (96) found higher parity was associated with higher BMI and higher prevalence of CVD risk factors. However, other studies have found the role of parity in postpartum weight retention unclear (99,100). While the strength of the association may be debated, it is widely accepted that parity is associated with greater adiposity and lower levels of HDL cholesterol (89,96), even decades after childbearing (101). As a result, increased parity appears to be an additional risk factor for developing atherosclerosis among females, beyond the presence of conventional risk factors (89). The biological mechanisms that may explain this association have been suggested to be a result of modified exposure to sex steroids during each pregnancy (89); however, the role of endogenous sex hormones in the development of atherosclerosis requires further exploration.

Conditions such as hypertension, diabetes, and obesity as they relate to parity have also been found to significantly contribute to atherosclerosis (102). Because the carotid arteries thicken and develop plaque build-up, blood flow is reduced and impairs the body's ability to provide oxygen and nutrients to the organs (57,103,104). When comparing parous (≥1 birth) and

nulliparous (no previous births) females for the Rotterdam Study (101), there was a 36% greater risk of carotid atherosclerosis for females who had 1-3 children with the risk increasing to 64% for females with ≥4 children. In addition, it has been found that cardiovascular risk factors such as diabetes and hypertension are more likely among parous females when compared with nulliparous females in later life (105).

Increased arterial wall thickness and lower carotid arterial distensibility have also been found with increased parity (102,105). It remains unclear at which level of parity the risk is greatest; evidence suggests that some relationships were found to be J-shaped with a nadir of risk at 1-2 births while others were found to be U-shaped with a nadir of risk at 3 births (80,92,102,106). Further, increased carotid arterial distensibility has been suggested to be a possible mechanism in the association of parity and coronary heart disease in later life whereby CHD prevalence is higher in multiparous (2+ births) females compared to only one live birth even after accounting for potential confounding factors (106). This evidence may suggest that the influence parity has on CVD risk may not be observed until later in life.

1.5.2 Socioeconomical Factors

While most research focuses on the physiological and biological changes that occur with multiple pregnancies to be the cause of increased cardiovascular risk, others have suggested a correlation of risk with socioeconomical factors such as the stressors that accompany rearing multiple children (92). In a study by Lawlor et al. (107), it was found that lifestyle risk factors (smoking, alcohol, and physical activity) associated with childrearing lead to obesity and, therefore, increased risk of developing CHD in both males and females. However, when adjusting for obesity and metabolic risk factors, the association was attenuated in both sexes,

although some association remained in females (107). In contrast, other research has found that parity is associated with carotid atherosclerosis, a risk factor for CVD, in both younger and older females but not in males, indicating that childbearing rather than childrearing may be the cause for increased cardiovascular risk among females (89). This suggests that there may be additional adverse effects of the physiological and biological mechanisms of pregnancy that are associated with increased cardiovascular risk.

1.6 Menopause & Cardiovascular Risk

The transition of menopause is characterized by a permanent cessation of menstruation (12 months) in females and typically occurs at the average age of 51 years (108), with levels of estrogens decreasing across perimenopause (109). Due to the significant hormonal changes that occur across perimenopause and with menopause, it is important to consider the influence this life event may have on cardiovascular risk. The risk of metabolic syndrome, a collection of heart disease risk factors, increases substantially during perimenopause and early menopause (110). Postmenopausal females are at a greater risk of hypertension, diabetes, weight gain, and insulin resistance when compared with premenopausal females (110).

However, in a study by Skilton et al. (89) the association between parity and atherosclerosis was not altered, even after adjusting for menopausal status. It has also been suggested that while hormonal alterations may be a possible mechanism explaining the association between higher CVD risk with increased parity, it is perhaps the repeated exposure to hormonal alterations causing an accumulation of physiological changes that occur with each additional pregnancy that may explain the association (111). While the specific role menopause

plays in the association between parity and cardiovascular risk requires further exploration, it is well-established that parity is an important factor to consider in predicting CVD risk.

1.7 Cardiovascular Health & Physical Fitness

Not only does physical inactivity increase the risk of developing conditions such as obesity, diabetes, and hypertension (112), but it has also been shown to be the most prevalent modifiable risk factor amongst Canadians with inactivity levels increasing with age (113). Further, females have been found to be more physically inactive (50%) when compared to males (45%) in ages 75+ (113).

Exercise is defined as structured and repetitive physical activity designed to maintain or improve physical fitness (114). Physical activity refers to bodily movement produced by skeletal muscles that result in energy expenditure (114), while physical fitness represents the capacity to achieve a certain performance standard (114). Cardiorespiratory fitness is one component of physical fitness and refers to the combined efficiency of the lungs, heart, vascular system, and muscles in the transport and use of oxygen during prolonged and strenuous exercise (114). Physical fitness and physical activity are inter-related; physical fitness can be used as an objective measure of recent physical activity patterns (114) and physical activity is a determinant of cardiorespiratory fitness (115). Physical fitness can be measured more objectively than physical activity using the metabolic equivalent of task (MET), a measure of energy expended during physical activity (114). Cardiorespiratory fitness can be measured using VO_2 max, a measure of maximal oxygen consumption during exhaustive exercise (116). While factors such as age, sex, current health, and genetics contribute to cardiorespiratory fitness, habitual physical activity levels is the main determinant (114).

High levels of physical activity and cardiorespiratory fitness have been found to be associated with lower cardiovascular and all-cause mortality (114). While physical activity and physical fitness have both shown to reduce cardiovascular risk, physical fitness is more influential in lowering CVD risk compared to physical activity (117). Increased physical fitness promotes reductions in blood pressure, total cholesterol, and waist circumference, with improvements in HDL cholesterol and glucose metabolism (118,119). With a reduction in these risk factors, chronic health conditions such as obesity, diabetes, and hypertension decrease, therefore promoting improved arterial stiffness (25,61,63) and decreased cardiovascular risk (120,121). While various modes of exercise reduce cardiovascular risk, aerobic exercise, specifically, has been found to be the most effective (121–123).

Regular aerobic exercise can improve cardiovascular health by several mechanisms. First, aerobic exercise increases NO bioavailability and reduces oxidative stress and inflammation thereby improving vascular smooth muscle cell relaxation (124,125). Second, aerobic exercise causes intrinsic changes of the arterial walls through an alteration of collagen and elastin resulting in reduced vascular resistance (126,127). These improvements in vascular function result in reductions in blood pressure, lipids, and BMI, as well as a reduced risk of cardiovascular events such as myocardial infarction and stroke (120,128,129).

With regular and consistent participation in aerobic exercise, physical fitness – particularly cardiorespiratory fitness – improves (130). In addition, it has been suggested that regular participation in aerobic exercise can not only prevent vascular stiffening, but also reverse the natural vascular stiffening that occurs with aging (121). It is important to note that the intensity at which aerobic exercise is completed influences the degree of vascular benefit with most studies supporting moderate to vigorous intensity aerobic training to be most effective

(114,122,131). Whether or not resistance training (RT) is able to significantly reduce cardiovascular risk remains unclear. Some studies have found RT to have no beneficial effects on arterial stiffness (122) while others have found RT to be associated with an increase in arterial stiffness (132,133). Additionally, a distinction between acute and chronic bouts of RT appears to play an influential role on blood pressure, whereby acute bouts of RT have been found to increase blood pressure and arterial stiffness (121,134). However, chronic RT has shown to reduce resting blood pressure (systolic and diastolic), improve insulin sensitivity, and decrease fat mass (135). Further exploration into the intensity and modality of RT is needed to determine the effect it may have in reducing CVD risk.

This evidence highlights the critical impact physical fitness has on the reduction of CVD risk through regular participation in aerobic-based physical activity. With reduced arterial stiffness, an improvement in cardiovascular risk will be observed.

1.8 Framingham Risk Score

Risk assessment is critical in the prevention and treatment of cardiovascular disease. The Framingham Risk Score (FRS) is a validated method of predicting an individual's 10-year risk of developing CVD (136). The FRS takes into account CVD risk factors such as smoking, systolic blood pressure, use of antihypertensive treatments, total and HDL cholesterol, age, and sex; if lipid information is unavailable, BMI can be used as an alternative (137). Risk is considered low if the FRS is less than 10%, moderate if it is between 10% and 19%, and high if it is 20% or higher (138). It has been found to reliability predict short-term risk for CVD for both males and females (139) and found to have good discrimination and calibration, indicating alignment of observed and predicted CVD events (136,140). While the FRS has been suspected of

underestimating CVD risk in females due to a lower short-term CVD risk but higher lifetime risk (139,141), the FRS was found to have good agreement among predicted and observed risks for males and females (142,143). With age, FRS increases due to advancing age being a risk factor for developing CVD and due to a greater burden of CVD risk factors (139). It is commonly used in primary care settings due to its ease of use and availability of health information within a clinic or office (140).

Other CVD risk prediction tools such as the CVD risk estimation algorithm developed by the Systematic Coronary Risk Evaluation (SCORE) has been found to accurately predict CVD risk (144); however, this algorithm only predicts fatal CVD, which may result in an underestimation of the total CVD burden (140). The Reynolds risk score was developed to predict CVD in females specifically and incorporates family history of CVD as well as high-sensitivity C-reactive protein in the algorithm (145). While the Reynold risk score takes into account similar risk factors as the FRS, it requires measurement of hemoglobin A_{1C} for those with diabetes (146) and does not have the option of using BMI if cholesterol information is unavailable. While it is has been found to provide an accurate CVD risk prediction (145,147), its implementation may be limited as it requires a blood specimen in order to accurately calculate an individual's CVD risk, while the FRS does not.

While the FRS is designed to predict CVD risk in asymptomatic individuals, it has also been tested for those already on treatment for CVD related risk factors (136). For individuals already receiving treatment for CVD risk factors such as diabetes or hypertension, the FRS was found to accurately predict risk for males and slightly overestimate risk for females (136). However, Chia et al. (136) suggested that it may not be a true overestimation of risk in females but rather a result of improved control and treatment of cardiovascular health in females over the

course of the last decade. Control of cardiovascular risk factors such as hypertension is lower among females compared to males (24,38) due to a history of underrepresentation of females in clinical trials and less aggressive treatment strategies (41).

1.9 Summary of Knowledge Gap

CVD risk factors are consistently proven to be associated with a greater rate of cognitive decline and an increased rate of cognitive and vascular impairment (11,15,36,148). While numerous cognitive domains are affected, reduced executive function has been found to be associated with higher CVD risk (11,148,149). The maintenance of cardiovascular health from mid to late life has shown to have a direct result on slowing cognitive decline later in life (16). Given that low levels of cardiovascular risk have been found to be associated with preservation of cognitive function for 10 years in older females (148), sex-specific life events such as childbearing must be considered when discussing cardiovascular and cognitive health in females. The impact of childbearing on both cardiovascular and cognitive health has been widely explored during pregnancy and postpartum (150,151). However, findings to date regarding the potential impact of parity on cardiovascular and cognitive health are equivocal. Further, how parity impacts cardiovascular and cognitive health long-term remains unclear.

Thus, this study examined the relationship between parity and cardiovascular risk in older females with mild cognitive impairment – individuals who are at risk for dementia. Additionally, this study also examined the relationship between parity and executive function in older females with mild cognitive impairment. For both relationships, the potential influence of physical fitness was also observed.

1.10 Research Objectives

Primary Objective:

Explore the relationship between parity and cardiovascular risk in older females with mild cognitive impairment.

Secondary Objectives:

To explore:

1. The influence of physical fitness on the relationship between parity and cardiovascular risk in older females with mild cognitive impairment.
2. The relationship between parity and executive function in older females with mild cognitive impairment.
3. The influence of physical fitness on the relationship between parity and executive function in older females with mild cognitive impairment.

2. METHODS

2.1 Ethical Approval: Ethical approval was obtained from the University of British Columbia's (UBC) Clinical Research Ethics Board (H15-02181; H15-00972). All participants provided written and informed consent before participating.

2.2 Study Design: We conducted a cross-sectional study of 104 community-dwelling, older adult females who live in Metro Vancouver, BC, Canada. Female participants from two ongoing randomized controlled trials, Reshaping the Path of Mild Cognitive Impairment by Refining Exercise Prescription (FACT) and Reshaping the Path of Vascular Cognitive Impairment with Resistance Training (RVCI), were used for analyses. The FACT and RVCI participants were assessed at baseline, mid-point (3 and 6 months, respectively), and trial completion (6 and 12 months, respectively); only baseline data were used for the analysis of this study. Assessments took place at the Research Pavilion at Vancouver General Hospital (VGH).

2.3 Recruitment: Participants were recruited from the community, the VGH Falls Prevention Clinic, the VGH Stroke Clinic, the VGH Geriatric Internal Medicine Teaching Clinic, and the UBC Hospital Clinic for Alzheimer Disease and Related Disorders (UBCH-CARD). Interested individuals were first screened by telephone to check for general eligibility according to the inclusion and exclusion criteria, and the Physical Activity Readiness Questionnaire (PAR-Q), a screening measure of physical readiness for exercise (152). Those who were deemed eligible were scheduled for a familiarization/screening assessment, where they were provided with additional information about the study. Each participant was informed of their confidentiality, potential risks of the study, and their right to withdraw from the study at any time. For

participants recruited after March 2020, the screening assessment was done via telephone to minimize in-person contact with respect to COVID-19 and informed consent was obtained electronically.

2.4 Participants & Sample Size: This study included 104 community-dwelling, older adult females from the participant pool of the two RCTs mentioned above. To estimate the number of individuals needed to detect a significant effect of parity on cardiovascular risk (i.e., primary objective), a statistical power of 70% and a probability of type 1 error (alpha) of 5% were chosen. According to previous literature examining the relationship between parity and CVD risk, we estimated a moderate effect size (92,153). The estimated predicted effect size of parity on cardiovascular risk was estimated to be Cohen's f of 0.25. Using G*power software, the sample size required was 102 participants, accounting for three covariates: PWV, CVD medications (yes/no), and estimated VO_2.

Inclusion criteria: 1) aged ≥ 55 years; 2) have subjective memory complaints, defined as the self-reported feeling of memory worsening with an onset within the last 5 years, as determined by interview and corroborated by an informant (154); 3) able to walk independently; 4) preserved general cognition as indicated by a Mini-Mental State Examination (MMSE) score of ≥ 22/30 and ≥ 20/30 for the RVCI and FACT studies, respectively, as well as a Montreal Cognitive Assessment (MoCA) score of < 26/30 for both studies; 5) scored ≤ 5/15 on the 15-item Geriatric Depression Scale (GDS); 6) completed high school education; 7) are community-dwelling; 8) live in their own home; 9) read, write, and speak English with acceptable visual and auditory acuity; and 10) in sufficient health to participate in the exercise programs. This was based on medical history and written recommendation by family physician.

Exclusion criteria: 1) have been diagnosed with Alzheimer's disease or other dementias; 2) have a chronic medical or neurological disorder or psychiatric illness; 3) smoke currently; 4) on any hormone therapy (estrogen, progesterone, or testosterone) in the last 24 months; 5) currently on heart disease medication (e.g., beta-blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors); 6) are planning to participate, or already enrolled in, a concurrent clinical drug or exercise trial; 7) engaged in moderate physical activity ≥ 1 time per week, or ≥ 60 minutes per week, in the 3 months prior to study entry; 8) clinically suspected to have neurodegenerative disease as the cause of MCI; and 9) at high risk for cardiac complications during exercise or unable to self-regulate activity or to understand recommended activity level.

2.5 Study Procedures: The study was a cross-sectional analysis of data obtained from participants at baseline from two RCTs, as described above. After eligibility was confirmed and informed consent was obtained, participants were invited to attend the in-person assessment session at which they were assessed with the instruments outlined below.

Demographics: We measured age in years, education level, standing height in centimeters, mass in kilograms, resting systolic and diastolic blood pressure, and resting heart rate during the assessment session. Each body measurement was completed twice and the average of two trials was used.

Health Status & History: We assessed the presence of comorbidities using the Functional Comorbidity Index (FCI), which is a questionnaire consisting of a variety of health conditions with the score equaling the total number of comorbidities present (155). Reproductive history information such as age of menopause and use of contraceptives were collected using the

Reproductive History Questionnaire (156). The standardized questionnaire was used to determine any current medications being taken.

Grip Strength: Grip strength was measured using a Jamar Hand Grip Dynamometer (157). From a seated position with feet flat, participants held their elbow at 90 degrees and into their side. Participants were instructed to squeeze the dynamometer handle as hard as they could until the assessor observed the number on the display no longer increasing and instructed them to stop. After each test, participants were instructed to switch hands and perform again until three complete tests had been completed on both the left and right sides. Verbal encouragement from the assessor was provided with each test. Reduced muscle strength as measured by grip strength can be indicative of higher physical frailty (158).

Global cognition: Global cognition was measured using the MMSE and the MoCA with lower scores indicating poorer cognitive performance (159–161). Both tests were rated on a 30-point scale, with a higher score indicating greater cognitive performance, and included tests of orientation, attention, memory, language and visual-spatial awareness (159,160)

Mobility: The Short Physical Performance Battery (SPPB) was used to measure functional mobility as well as gait speed. The SPPB assessed balance, usual gait speed, and strength with each component having a possible score range of 0 (inability to perform the task) to 4 (optimum performance), for a maximum score of 12 points (162). To assess balance, participants were asked to stand in side-by-side, semi-tandem, and tandem stands for up to 10 seconds each stand (162). To assess gait speed, participants were asked to walk at their usual pace along a 4-metre path with their gait speed (m/s) calculated as the best of two trials. To assess strength, participants were asked to stand from a seated position five times consecutively

as quickly as possible without the use of their arms. An overall score of <9/12 predicted subsequent disability (163).

Outcomes: Framingham Risk Score, parity, physical fitness, pulse wave velocity, and executive function were measured across all participants.

Framingham Risk Score: The FRS is a validated tool to predict an individual's 10-year cardiovascular disease (CVD) risk and is derived as a percentage (138). The risk score was calculated using an equation that took into account sex, age, blood pressure, hypertension, smoking, diabetes, total cholesterol, and HDL cholesterol; BMI was used as a substitute when cholesterol information was unavailable (164). The Intake Form was used to collect sex, age, and BMI. The presence of hypertension and diabetes were collected from the Functional Comorbidity Index (FCI) (155). The standardized questionnaire was used to collect smoking status. Total cholesterol and HDL cholesterol levels were collected from the participant's baseline blood tests. Resting blood pressure was measured during the assessment session. CVD risk was considered low if the FRS was <10%, moderate if it was 10-19%, and high if it was ≥ 20% (138).

Parity: The number of live births was determined using the Reproductive Health Questionnaire. The Reproductive History Questionnaire consisted of 12 questions; this varied dependent on answers to certain questions as there were follow-up questions included to gather further information. The self-report questionnaire aimed to obtain information regarding participants' menstrual cycle, pregnancy, hormone therapy, menopause, and number of children. Using the questionnaire, the number of children was determined by asking if the participant had been pregnant, if so, how many times had they been pregnant, and asked if each pregnancy lasted

longer than 6 months. Participants were also asked how many biological children they had. All participants reported the same number of pregnancies lasting longer than 6 months as they did for number of biological children. Due to ethical reasons, we were unable to collect information regarding incomplete pregnancies, gestational health conditions, or fertility issues. Individuals who had given birth to three, four, or five children were grouped into one category to allow for equal distribution among parity groups. The categories for parity were 0, 1, 2, 3+ births.

Physical Fitness: The 400-Metre Walk Test (400mWT) and the Six Minute Walk Test (6MWT) were used to assess physical fitness levels in the FACT and RVCI studies, respectively. Both tests can be used to estimate submaximal cardiorespiratory fitness (165–167). Due to the clinical and geriatric nature of the population in this study, maximum oxygen consumption (VO_2) protocols would not be appropriate. Self-paced walking tests such as the 400mWT and the 6MWT are reliable, non-invasive measures used to estimate VO_2 and are valid indicators of cardiorespiratory fitness in both males and females aged 60+ years (165–167).

The 400mWT involved having the participant walk nine laps of approximately 44 metres consecutively. The assessor familiarized the participant with the walking path before beginning the test. The participant was then instructed to walk as quickly as they could without running and was advised that they could take a break, if needed. The assessor recorded the total number of laps walked and notified the participant once the target had been reached. The test was complete once the participant walked 400 metres. The total time taken to complete the 400-metre course was recorded. Participant's blood pressure was measured before the walk and immediately following test completion.

The 6MWT involved having the participant walk around a specified path repeatedly for six minutes. The assessor familiarized the participant with the walking path before beginning the

test. The participant was then instructed to walk as quickly as they could without running and was advised that they could take a break, if needed. The assessor recorded the total number of metres walked throughout the duration of the test and notified the participant once the duration had been reached. The test was complete once the participant completed six minutes of walking. The total distance walked in six minutes was recorded. Participant's blood pressure was measured before the walk and immediately following test completion.

If a participant requested a break for either test, the duration of the break was recorded and included in the final time; the number of breaks taken was also recorded. The assessor walked closely behind the participant throughout the duration of both tests to ensure safety and updated the participant on their progression throughout the test.

To determine speed of movement, metres walked and time elapsed were taken from both the 6MWT and the 400mWT and converted to metres per minute (m/min). Using m/min, we calculated a VO_2 estimation value by using the following formula: $VO_2 = (0.1 * speed) + (1.8 * speed * grade) + 3.5$ (168).

Pulse Wave Velocity: Carotid-femoral pulse wave velocity (PWV) was measured as an indicator of arterial stiffness using the Complior Analyse™ software. PWV is considered the gold standard of non-invasive arterial stiffness measurement (55,169,170). Recent evidence has shown that cf-PWV provides a more accurate estimate of arterial stiffness in comparison to other common methods of measurement such as brachial-radial PWV (baPWV) or augmentation index (125). PWV values range between 8.7 and 13.5 m/s for those aged 60+ years, with a higher PWV value indicative of greater cardiovascular risk (55). A lower Cf-PWV value (below 11 m/s) is considered 'normal' and indicates better health where as values above 11 m/s are considered

'high normal' (55). Participants' values were compared against norms for their sex and age and categorized into respective blood pressure risk levels.

PWV was measured by dividing the distance between the carotid and femoral arteries by the transit time of the pulse between these two landmarks. Participants were asked to lie supine on an exam table and rest in a quiet, temperature-controlled room for five minutes prior to the PWV measurement in order to stabilize the heart rate and blood pressure. The assessor launched the Complior Analyse ™ software and entered the participants' details such as the ID code, age, and sex. After the assessor palpated the common carotid and ipsilateral femoral arteries the distance between these two landmarks was measured using a measuring tape. This distance was entered into the software program while the participants' blood pressure was obtained and entered. The assessor then positioned a pressure sensor on the carotid landmark previously established while holding a second pressure sensor on the femoral landmark. Sensors were placed directly on the skin and held steady by the assessor while the participant was instructed to remain still until the software indicator turned green – indicating 10 consecutive wave forms were collected. If the participant moved during the assessment, the testing procedure was repeated. Once the Complior software indicated that the trial was complete, the sensors were removed from the participant and sanitized appropriately. A PWV analysis summary was automatically generated. If the carotid-femoral (CF) tolerance value – a quality parameter provided by the Complior software – was greater than 5 m/s, the assessment was re-administered until the CF tolerance was below 5 m/s (171).

Executive Function: Executive function was measured by the Digit Symbol Substitution Test (DSST). This test measured processing speed, working memory, and visuospatial attention (172). The test required the participant to match symbols to numbers according to a key provided

at the top of the page as quickly as possible. The score was equal to the number of correct symbols matched within a 90 second timeframe (173). A higher score indicated better cognitive performance (172).

2.6 Statistical Analyses: Statistical analyses were conducted using SPSS (Version 27.0.1.0). Descriptive statistics were reported for the variables of interest. Outliers were defined as any data points exceeding 3 standard deviations from the mean.

A one-way analysis of covariance (ANCOVA) was performed to assess whether there were differences in CVD risk, as measured by the Framingham Risk Score, among the different levels of parity (i.e., 0, 1, 2, and 3+), controlled for PWV, CVD medications, and estimated VO_2. A post hoc analysis with Bonferroni correction was conducted to determine differences between the levels of parity. The overall alpha was set at < 0.05.

To assess whether physical fitness moderated the relationship between parity and FRS, a linear regression analysis was performed with physical fitness, measured by VO_2 estimation value, and the interaction term of parity x physical fitness included in the model.

A one-way ANCOVA was performed to assess whether there were differences in executive function, as measured by the Digit Symbol Substitution Test, among the different levels of parity (i.e., 0, 1, 2, and 3+), controlled for PWV, CVD medications, estimated VO_2, and MoCA. A post hoc analysis with Bonferroni correction was conducted to determine differences between the levels of parity.

To assess whether physical fitness moderates the relationship between parity and DSST, a linear regression analysis was performed with physical fitness, measured by estimated VO_2, and the interaction term of parity x physical fitness included in the model.

3. RESULTS

3.1 Descriptive Statistics

Table 1 reports all baseline characteristics separated by parity level. The sample size of females who had given birth to one child was lowest, with only 15 participants reporting giving birth to one child. Further, parity at one child had the lowest FRS and performed the lowest in global cognition and executive function. Females who had given birth to 3+ children had the highest mean age as well as the highest FRS. Females who had not given birth to a child had the youngest mean age with the highest scores on the MoCA and DSST measures.

Table 1. Baseline characteristics separated by parity level.

Variable[ǂ]	Parity 0 *n*=40 Mean (SD)	Parity 1 n=15 Mean (SD)	Parity 2 n=27 Mean (SD)	Parity 3+ n=22 Mean (SD)	Sample n=104 Mean (SD)	*p-value*
Age (years)	75.70 (5.50)	76.93 (6.81)	76.04 (4.17)	77.00 (7.99)	76.24 (5.96)	0.825
Height (cm)	158.98 (9.48)	157.72 (7.99)	158.24 (7.29)	156.04 (7.68)	157.98 (8.33)	0.617
Weight (kg)	68.22 (16.79)	65.86 (15.30)	64.95 (14.79)	68.22 (17.02)	67.03 (15.97)	0.834
cf-PWV (m/s)	9.22 (2.23)	8.41 (2.22)	9.96 (2.57)	9.63 (2.61)	9.38 (2.42)	0.224
Estimated VO2 (mL/kg/min)	11.39 (1.79)	10.97 (1.51)	11.72 (2.08)	11.49 (1.55)	11.43 (1.78)	0.633
MoCA (/30)	22.18 (2.64)	20.13 (4.49)	21.89 (2.55)	21.14 (4.39)	21.59 (3.38)	0.206
MMSE (/30)	27.65 (1.63)	27.13 (2.00)	27.26 (1.79)	27.27 (2.19)	27.39 (1.83)	0.729
Education, n (%)						0.798
Less than grade 9	0 (0)	0 (0)	0 (0)	1 (4.5)	1 (1)	
Grades 9-13 without certificate or diploma	2 (5.0)	0 (0)	1 (3.7)	1 (4.5)	4 (3.8)	
Highschool certificate	3 (7.5)	2 (13.3)	4 (14.8)	0 (0)	9 (8.7)	
Trades/professional certificate or diploma	4 (10.0)	1 (6.7)	4 (14.8)	3 (13.6)	12 (11.5)	
Some university certificate or diploma	10 (25.0)	3 (20.0)	5 (18.5)	3 (13.6)	21 (20.2)	
University degree	21 (52.5)	9 (60.0)	13 (48.1)	14 (63.6)	57 (54.8)	
BMI (kg/m^2)	26.93 (6.04)	26.50 (6.33)	25.86 (5.34)	27.75 (5.06)	26.76 (5.67)	0.708
Systolic blood pressure (mmHg)	136.67 (19.42)	122.33 (19.03)	124.93 (12.30)	119.36 (9.62)	127.89 (17.38)	< 0.001
Diastolic blood pressure (mmHg)	80.25 (12.28)	74.67 (9.82)	74.37 (8.83)	71.50 (8.31)	76.07 (10.78)	0.011
HDL cholesterol (mg/dl)	66.85 (17.54)[a]	67.25 (18.60)[b]	70.51 (21.39)	70.38 (21.52)[c]	68.63 (19.38)	0.860

Variable[ǂ]	Parity 0 *n*=40 Mean (SD)	Parity 1 n=15 Mean (SD)	Parity 2 n=27 Mean (SD)	Parity 3+ n=22 Mean (SD)	Sample n=104 Mean (SD)	*p-value*
Total cholesterol (mg/dl)	196.33 (54.50)[a]	195.57 (43.91)[b]	192.32 (37.99)	217.19 (47.15)[c]	199.08 (47.64)	0.347
Currently taking anti-hypertensive medication, n (%)	14 (35.0)	3 (20.0)	9 (33.3)	14 (63.6)	65 (62.5)	0.625
Diabetes mellitus, n (%)	4 (10)	2 (13.3)	5 (18.5)	5 (22.7)	16 (15.4)	0.561
Smoker, n (%)	13 (32.5)	4 (26.7)	4 (14.8)	7 (31.8)	28 (26.9)	0.405
Functional Comorbidity Index (/21)	4.10 (2.02)	3.67 (2.13)	3.56 (1.78)	4.00 (2.56)	3.88 (2.09)	0.729
Short Physical Performance Battery (/12)	10.25 (1.35)	10.00 (1.65)	10.30 (1.10)	10.45 (1.50)	10.27 (1.36)	0.802
Gait Speed (m/s)	1.17 (0.24)	1.14 (0.25)	1.21 (0.21)	1.20 (0.25)	1.19 (0.23)	0.763
Grip Strength (kg)	22.73 (4.13)	21.65 (4.88)	24.68 (3.66)	23.45 (4.22)	23.23 (4.22)	0.114
Age of Menopause (years)	48.85 (6.07)	52.07 (3.26)	48.89 (4.80)	47.77 (8.26)	49.10 (6.06)	0.192
Previously took oral contraceptives, n (%)	25 (62.5)	7 (46.7)	23 (85.2)	15 (68.2)	70 (67.3)	0.064

[a] n=37; missing data for 3 participants as they did not consent to blood tests
[b] n=12; missing data for 3 participants as they did not consent to blood tests
[c] n=18; missing data for 4 participants as they did not consent to blood tests
[d] n=38; 2 data points excluded as outliers
[e] n=12; 3 data points excluded as outliers
[f] n=24; 3 data points excluded as outliers
[g] n=21; 1 data points excluded as an outlier
[h] n=13; 2 data points excluded as outliers
[i] n=26; 1 data point excluded as an outlier
[j] n=20; 2 data points excluded as outliers
ǂ MoCA = Montreal Cognitive Assessment; a lower score is indicative of poorer global cognition; MMSE = Mini-Mental State Examination; a lower score is indicative of poorer global cognition; cf-PWV = carotid femoral pulse wave velocity; BMI = body mass index; HDL = high-density lipoprotein.

Table 2. Outcome variables separated by parity level.

Variable[ǂ]	Parity 0 *n*=40 Mean (SD)	Parity 1 n=15 Mean (SD)	Parity 2 n=27 Mean (SD)	Parity 3+ n=22 Mean (SD)	Sample n=104 Mean (SD)	*p-value*
FRS (%)	11.00 (5.85)	9.11 (4.29)	13.58 (7.82)	16.07 (6.74)	12.47 (6.76)	0.004
DSST	45.94 (9.79)[a]	35.93 (9.64)	45.80 (8.11)[b]	41.20 (12.39)[c]	43.35 (10.49)	0.006

[a] n=36; missing data for 4 participants due to DSST measure being implemented after baseline assessments
[b] n=25; missing data for 2 participants due to DSST measure being implemented after baseline assessments
[c] n=20; missing data for 2 participants due to DSST measure being implemented after baseline assessments
[ǂ] FRS = Framingham risk score; a lower FRS is indicative of lower CVD risk; DSST = Digit Symbol Substitution Test; a lower DSST score is indicative of poorer executive function

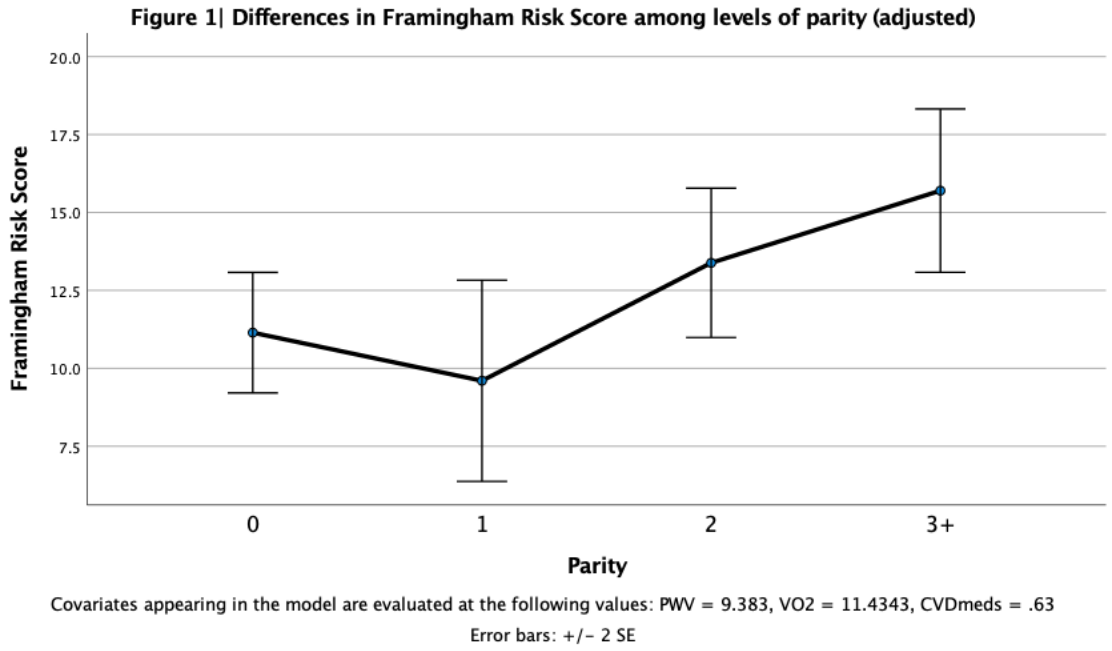
3.2 Differences in Cardiovascular Risk Among Levels of Parity

Approximately 16 data points for the cf-PWV were greater than 3 standard deviations above the mean and were excluded from the final analyses. For the 10 participants missing cholesterol data, BMI data was used in the calculation for FRS. After controlling for cf-PWV, estimated VO_2, and CVD medications, significant differences in the FRS as a function of parity were found ($F(3, 97) = 3.82$, $p = 0.012$) (**Table 3**). Specifically, post hoc comparisons demonstrated significant differences in FRS between parity levels 0 and 3+ ($p = 0.038$), as well as 1 and 3+ ($p = 0.026$). We observed a J-shaped relationship such that females who had given birth to 3+ children had the highest cardiovascular risk when compared to nulliparous and primiparous females (**Figure 1**).

Table 3. Results of the ANCOVA for cardiovascular risk as measured by FRS among levels of parity.

Source	Sum of Squares	df	Mean Square	F	*p*
cf-PWV	235.77	1	235.77	6.32	0.014
Estimated VO_2	9.53	1	9.53	.256	0.614
CVD medications	93.31	1	93.31	2.50	0.117
Parity	426.74	3	142.25	3.82	0.012
Error	20880.50	97	37.281		
Total	4710.40	104			

Figure 1. Differences in Framingham risk score among levels of parity (adjusted).



3.3 Physical Fitness as a Moderator of the Relationship between Parity and Cardiovascular Risk

After controlling for cf-PWV and CVD medications, physical fitness, as measured by estimated VO_2, was not found to significantly moderate the relationship between parity and cardiovascular risk, as measured by FRS (R^2 change = .000, p = 0.926) (**Table 4**).

Table 4. Moderation analysis of physical fitness for the relationship between parity and cardiovascular risk as measured by FRS.

	Total R^2	R^2 Change	B (SE)	β	*t*	*p*
Model 1: Main effects	0.107	0.107				
Parity			1.740 (0.633)	0.306	3.251	0.002
Estimated VO_2			-0.512 (0.358)	-0.135	-1.429	0.156
Model 2: Covariates	0.209	0.101				
cf-PWV			0.746 (0.264)	0.267	2.827	0.006
CVD meds			2.065 (1.322)	0.149	1.562	0.121
Model 3: Interaction term	0.209	0.000				
Parity x Estimated VO_2			0.028 (0.306)	0.008	0.093	0.926

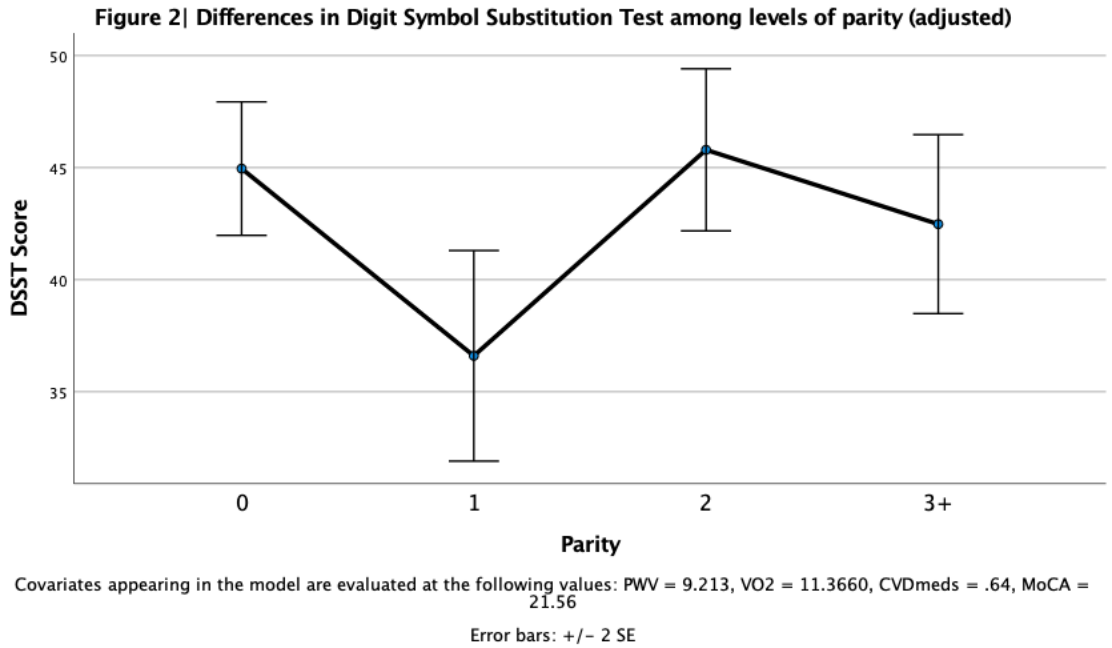
3.4 Differences in Executive Function Among Levels of Parity

Eight data points for the DSST were missing due to the measure being introduced after the participants' baseline assessments and were excluded from the final analyses. After controlling for cf-PWV, estimated VO_2, CVD medications, and MoCA, significant differences in DSST scores among levels of parity were found ($F(3, 88) = 3.67$, $p = 0.015$) (**Table 5**). Specifically, post hoc comparisons demonstrated significant differences in DSST scores between parity levels 0 and 1 ($p = 0.021$), as well as 1 and 2 ($p = 0.019$). We observed a nadir of executive function for primiparous females when compared to females having given birth to zero and two children (**Figure 2**).

Table 5. Results of the ANCOVA for executive function as measured by DSST among levels of parity.

Source	Sum of Squares	df	Mean Square	F	*p*
cf-PWV	495.56	1	495.56	6.37	0.013
Estimated VO_2	3.66	1	3.66	0.047	0.829
CVD medications	271.64	1	271.64	3.49	0.065
MoCA	859.62	1	859.62	11.05	0.001
Parity	856.87	3	285.62	3.67	0.015
Error	6844.57	88	77.78		
Total	190900.00	96			

Figure 2. Differences in DSST score among levels of parity (adjusted).



3.5 Physical Fitness as a Moderator of the Relationship between Parity and Executive Function

After controlling for cf-PWV, CVD medications, and MoCA, physical fitness, as measured by estimated VO_2, was not found to significantly moderate the relationship between parity and executive function, as measured by DSST (R^2 change = .001, p = 0.687) (**Table 6)**.

Table 6. Moderation analysis of physical fitness for the relationship between parity and executive function as measured by DSST.

	Total R^2	R^2 Change	B (SE)	β	*t*	*p*
Model 1: Main effects	0.065	0.065				
Parity			-1.029 (0.893)	-0.116	-1.151	0.253
Estimated VO_2			1.366 (0.583)	-0.135	2.342	0.021
Model 2: Covariates	0.265	0.199				
cf-PWV			-0.757 (0.421)	-0.173	-1.796	0.076
CVD meds			-4.285 (2.069)	0.149	-2.071	0.041
MoCA			1.123 (0.291)	0.363	3.856	<.001
Model 3: Interaction term	0.266	0.001				
Parity x Estimated VO_2			-0.195 (0.482)	-0.038	-0.404	0.687

4. DISCUSSION

This study found significant differences in cardiovascular risk as well as executive function as a function of parity (0, 1, 2, 3+ births). Results of the moderation analyses showed that physical fitness did not moderate the relationship between parity and cardiovascular risk nor did it moderate the relationship between parity and executive function in older females with mild cognitive impairment.

4.1 Parity & Cardiovascular Risk

Our findings suggest that there are significant differences in cardiovascular risk, as measured by FRS, as a function of parity in older females with mild cognitive impairment, after accounting for PWV, CVD medications, and physical fitness. Specifically, we observed a J-shaped pattern of risk with significant differences existing between females having one birth and females having three or more births, as well as between females having zero births and females having three or more births. Parikh et al. (72) found a similar non-linear J-shaped pattern between parity (0, 1, 2, 3, 4, 5+ births) and later-life maternal CVD but with a nadir of risk with females having two births. Similarly, Lawlor et al. (107) observed the same pattern between parity (0, 1, 2, 3, 4, 5+ births) and coronary heart disease with a nadir of risk with females having two births. Both studies accounted for socioeconomic factors with no changes in the overall results. A study by Shen et al. (106) found CHD prevalence to be lowest among primiparous females compared with multiparous females, however, they did not include nulliparous females in their analysis. While we found CVD risk to be lowest among primiparous females as well, our measure of risk considered numerous factors, rather than prevalence. A meta-analysis including 10 cohort studies and over 3 million females by Li et al. (111) identified a significant

relationship between parity and CVD risk with a 16% greater risk among parous females compared to nulliparous females. While our findings found significant differences in CVD risk among females having zero and three or more births, this study only reviewed results based on parity status (nulliparous versus parous) and did not distinguish among levels of parity.

Why parity may be related to CVD risk remains unclear (111,174) but several explanatory factors have been proposed. Repeated pregnancies could result in physiological and cardiometabolic changes such as weight gain, hyperlipidemia, or endothelial dysfunction, which may increase CVD risk in later life among parous females compared with nulliparous females (105,111,174). Others have suggested that multiparity could result in repeated exposure to hormone alterations, which may lead to changes in glucose metabolism and increased insulin sensitivity, leading to a greater risk of developing CVD (101,111,175). Although there have been inconsistent findings regarding the level of parity at which CVD risk is greatest, the importance of taking reproductive health into consideration when evaluating CVD risk in older females in later life is well-established.

4.2 Physical Fitness as a Moderator of the Relationship between Parity & Cardiovascular Risk

Contrary to our hypothesis, we found that physical fitness did not moderate the relationship between parity and CVD risk in older females after accounting for PWV and CVD medications. Previous findings have established a significant inverse relationship between physical fitness and CVD risk (115), with higher levels of physical fitness reducing CVD risk as well as all-cause mortality (114,115,117).

A potential explanation for these opposing findings could lie in the use of the walking tests as measures of physical fitness, which may be influenced by mobility or functional limitations and as a result, may not reflect true estimates of physical fitness. Within this sample, primiparous females had the lowest mean physical fitness as well as mobility (**Table 1**), as measured by estimated VO_2 and SPPB, respectively. Poor performance on the 400-metre walking test as well as the SPPB has been found to be suggestive of prevalent or impending mobility limitations (162,166). It is plausible that poorer mobility impacting performance on the walking tests could, in part, explain why physical fitness did not moderate the relationship between parity and CVD risk.

4.3 Parity & Executive Function

We found significant differences in executive function as a function of parity in older females with mild cognitive impairment after accounting for PWV, CVD medications, physical fitness, and global cognition. While not significant, we observed primiparous females having the poorest executive function and females having two births having the highest executive function. There were significant differences in executive function between females having zero births and females having one birth as well as females having one birth and females having two births. Specifically, females having either zero or two births showed better executive function than females having one birth. Findings to date regarding the potential impact of parity on executive functions are equivocal. Ryan et al. (151) found no significant differences in executive function among levels of parity. However, they did find significant differences in visual memory with nulliparous females having better visual memory when compared with parous females. A study by Read & Grundy (150) found a U-shaped relationship between parity and cognition,

specifically memory and executive function, whereby females with low (0-1 child) and high (3+ children) parity experienced faster cognitive decline over an 8-year period compared to females with medium (2 children) parity. This aligns with our findings as we found lowest executive function existing among females with one child.

The differences in executive function as a function of parity could be related to vascular damage within the brain, as a result of CVD risk factors (23). Specifically, CVD risk factors such as hypertension and hypercholesterolemia leading to greater risk of atherosclerosis and hypoperfusion to the brain have been suggested as contributing factors (176). Additionally, hypoperfusion of the brain caused by these risk factors can cause an accumulation of a peptide called amyloid-beta, leading to an accumulation of plaques and tangles, which is a key component in the pathology of AD (22,23).

Given the established inverse relationship between cardiovascular health and cognition, including executive function (36,177,178), we did not expect to find that primiparous females were at the lowest risk of CVD while also having the lowest executive function. However, within this study sample, primiparous females were observed to have the lowest mean SPPB scores and weakest grip strength when compared with other levels of parity (**Table 1**). Reduced functional mobility and strength, as measured by the SPPB and grip strength measures, respectively, both suggest possible physical frailty (158,163). Increased physical frailty may provide insight into why we observed reduced levels of executive function despite improved cardiovascular health among primiparous females, as reduced physical frailty has been shown to be related to poorer cognitive impairment as well as executive function specifically (12).

4.4 Physical Fitness as a Moderator of the Relationship between Parity & Executive Function

Contrary to our hypothesis, we found that physical fitness did not moderate the relationship between parity and executive function in older females after accounting for PWV, CVD medications, and global cognition. Previous findings have shown higher levels of physical fitness to contribute to better executive function in older adults (116,179).

Functional and mobility limitations, as measured by the SPPB, may provide insight into why physical fitness did not moderate the relationship between parity and executive function within this sample. As previously stated, mobility was poorest among primiparous females as indicated by the lowest SPPB score (**Table 1**) when compared with other levels of parity, suggesting the possibility that reduced mobility may contribute to underestimated estimates of physical fitness. Further, Guralnik et al. (162) reported that walking speed is a predictor of mobility impairment, thus, lower physical fitness among primiparous females may be indicative of possible mobility impairments as a result of slower performance on the walking tests.

Another possible explanation for physical fitness not significantly moderating the relationship between parity and executive function could be that the sample is comprised of females with mild cognitive impairment. Given that mild cognitive impairment is related to decreased walking speed (180,181), it is possible that this could have contributed to reduced physical fitness estimates as a result of slower performance on the walking tests.

5. LIMITATIONS

Due to the cross-sectional design and specific population comprised of individuals with mild cognitive impairment, conclusions about the causality and generalizability cannot be made. Further, there are numerous factors that may have a cumulative impact on cognitive health throughout a lifetime that could not be controlled for in this study such as age at first childbirth, social support in childrearing, and socioeconomic status, all of which have been found to influence cognitive health long-term (150). In this study, we used DSST which measures executive function, working memory, processing speed, and visuospatial attention (172,173). As a result, we were unable to assess whether the level of parity had differential impacts on specific executive processes, such as set-shifting, working memory, and response inhibition (12,172,180). Due to the distribution in this sample being lower among the primiparous group compared with nulliparous and multiparous groups, we have more uncertainty in our estimates that might lower the overall power of the test (182). Therefore, our findings may underestimate the true differences in cardiovascular risk and executive function amongst each level of parity. To determine physical fitness, we used a formula-based calculation based off performance on walking tests. While indirect calorimetry is considered the gold standard method of energy expenditure measurement (183), the walking method used in this study allowed for safe and reliable measurement of submaximal fitness levels given the older age and clinical nature of our sample (165,166). Lastly, we were unable to collect information on pregnancy-related health conditions such as health complications, miscarriages, or fertility problems, which may provide information regarding maternal health. Pregnancy-related health conditions have been found to be significantly associated with a higher risk of developing maternal cardiovascular risk factors (184,185). For example, females with a history of preeclampsia have a 2.4-times higher risk of

developing future diabetes, a 3.7-times higher risk of developing future hypertension, a 2.2-times higher risk of future coronary heart disease, and a 1.8-times higher risk of stroke in later life (185,186). Further, lack of parity in nulliparous females and lower parity in primiparous females may be related to health conditions impacting fertility which could potentially impact cardiovascular health and cognition (187). Future studies with a longitudinal design whereby researchers could observe health throughout pregnancies and into later life are needed to determine the role maternal health has on cardiovascular risk and cognition long-term.

6. CONCLUSION

Cardiovascular risk was lowest among primiparous females compared with multiparous females and yet, executive function was lowest among primiparous females and highest among females having given birth twice. Physical fitness did not moderate the relationship between cardiovascular risk and parity nor did it moderate the relationship between parity and executive function. Future work should explore the impact maternal health has in influencing cardiovascular and cognitive health in later life.

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