

**THE EFFECT OF MENOPAUSAL TRANSITION ON BODY COMPOSITION,  
CARDIOMETABOLIC RISK FACTORS, PHYSICAL ACTIVITY AND  
CARDIORESPIRATORY FITNESS**

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## ABSTRACT

Menopause transition is a natural process in a woman's life associated with altered body fat distribution, increased cardiometabolic risk, and the presentation of vasomotor symptoms including hot flashes and night sweats. A 5-year observational, longitudinal study (MONET: Montreal Ottawa New Emerging Team), was performed to document the effect of menopause transition on body composition and cardiometabolic risk factors. Initially, the study included 102 healthy non-obese premenopausal women between the age of 47 and 55 years. By the end of year 5, 91 women completed the study, 4% were still premenopausal, 29% were perimenopausal and 67% became postmenopausal. The major finding of the first study was that the increases in body fat mass and visceral fat in our cohort of non-obese women followed through the menopause transition were independent of the increase in body weight. Furthermore, these changes in body composition and body fat distribution were not associated with cardiometabolic deteriorations. We further examined whether specific factors such as reporting vasomotor symptoms (hot flashes and/or night sweats), exaggerated exercise systolic blood pressure, physical activity levels and cardiorespiratory fitness, may be associated with adiposity, body fat distribution and cardiometabolic profile. Overall, women that experienced vasomotor symptoms (paper 2) or presented an exaggerated exercise systolic blood pressure (paper 3), did not present any alterations in their body composition, body fat distribution and cardiometabolic profile compared to asymptomatic women and participants with normal blood pressure response to exercise, respectively. Furthermore, exaggerated exercise systolic blood pressure was not predictive of future hypertension after a 5-year follow-up throughout menopause transition. On the other hand, total volume of physical activity was not linked with measures of a cardiometabolic profile,

cardiorespiratory fitness appeared to have the greatest cardioprotective effect (paper 4). Therefore, in generally healthy physically active non-obese premenopausal women, the menopause transition does not generally alter cardiometabolic risk factors, and suggests that cardiorespiratory fitness may have greater cardiometabolic protective effects in this cohort.

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**LIST OF ABBREVIATIONS**

ACSM	American College of Sports Medicine
APO	Apolipoprotein
AScF	Abdominal Subcutaneous Fat
BMI	Body Mass Index
BP	Blood Pressure
CHD	Coronary Heart Disease
CRF	Cardiorespiratory Fitness
CRP	C-Reactive Protein
CT	Computed Tomography
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DEXA	Dual-Energy X-ray Absorptiometry
EE	Energy Expenditure
EBP	Exercise Blood Pressure
EDBP	Exercise Diastolic Blood Pressure
ER	Estrogen Receptors
ESBP	Exercise Systolic Blood Pressure
FM	Fat Mass
FSH	Follicle-stimulating Hormone
HDL-C	High-Density-Lipoproteins Cholesterol
HOMA-IR	Insulin Resistance Homeostasis Model Assessment
HRR	Heart Rate Ratio

HT	Hypertension
Kcal	Kilo Calorie
Kg	Kilogram
LDL-C	Low-Density-Lipoproteins Cholesterol
LH	Luteinizing Hormone
LPL	Lipoprotein Lipase
MET	Metabolic Equivalent
mmHg	Millimeter of Mercury
mmol/L	Millimoles per Liter
MONET	Montreal Ottawa New Emerging Team
N	Number
PA	Physical Activity
PAEE	Physical Activity Energy Expenditure
RHT	Replacement Hormone Therapy
RMR	Resting Metabolic Rate
SBP	Systolic Blood Pressure
SWAN	Study of Women's Health Across the Nation
T2D	Type 2 Diabetes
TC	Total Cholesterol
TG	Triglycerides
VF	Visceral fat
VMS	Vasomotor Symptoms
VO <sub>2</sub> peak	Peak Oxygen Consumption in mlO <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup>

VO <sub>2</sub> R	Maximum Oxygen Uptake Reserve
WC	Waist Circumference
WHR	Waist-to-Hip ratio

## CHAPTER 1

### 1. INTRODUCTION

It is well established that cardiovascular disease (CVD) is a leading cause of mortality in developed countries<sup>1</sup>. Annually, CVD is responsible for 30 percent of deaths worldwide<sup>2</sup> and in women, it is the leading cause of death. Half a million women die of CVD each year and most of them are asymptomatic<sup>3</sup>. Many well-established cardiometabolic risk factors have been identified including obesity, dyslipidemia, physical inactivity, type 2 diabetes (T2D) and hypertension<sup>4</sup>. Depending on the nature and/or the number of factors, the individual risk of CVD may vary from low to high<sup>5</sup>. Premenopausal women are known to have a lower incidence of CVD compared to age matched men and postmenopausal women<sup>6,7</sup>. However, after menopause women have an accelerated risk for developing higher total fat mass, abdominal obesity, insulin resistance, dyslipidemia, and T2D, which seems to increase in the presence of menopausal symptoms<sup>6</sup>. It is thus possible that the menopause transition *per se* increases risk of CVD in women.

Regular physical activity (PA), defined as a form of leisure and non-leisure body movements produced by the skeletal muscles, has a positive influence on the cardiometabolic risk of CVD<sup>8</sup>. Level of regular PA was demonstrated to be inversely proportional with the risk of CVD<sup>9,10</sup>. On the other hand, exercise is defined as a form of leisure-time PA that is planned, structured and repetitive<sup>10</sup>. The practice of regular PA or exercise, either light or moderate, is associated with a decreased prevalence of CVD and the rate of CVD mortality<sup>9</sup>. Notably, the more PA that is practiced, the lower is the CVD risk compared to sedentary individuals<sup>8,9</sup>.

Cardiorespiratory fitness (CRF), defined as maximal aerobic capacity ( $\text{VO}_2$  max or  $\text{VO}_2$  peak) measurements, is an independent predictor of the risk of death and cardiac events among asymptomatic women<sup>11</sup>. Low CRF is an independent risk factor for CVD and is also associated with an increased risk of metabolic syndrome<sup>12,13</sup>. In addition, fit individuals have lower rates of cardiometabolic health disturbances than those who are unfit<sup>14</sup>.

In this dissertation, we will provide more evidence on the associations between menopause status, vasomotor symptoms (VMS) and exaggerated exercise systolic blood pressure on body composition, abdominal fat as well as cardiometabolic risk factors. As well as, the respective protective role of PA and CRF during menopause transition on cardiometabolic risk factors will be investigated. The primary objective is to examine the changes in body composition and cardiometabolic risk factors in non-obese women going through the menopause transition (paper 1). The secondary objective is to compare body composition, body fat distribution, and cardiometabolic risk factors in non-obese premenopausal women with and without VMS; to determine the influence of PA levels and intensity on the prevalence of VMS throughout the menopause transition (paper 2). The tertiary objective is to investigate if an exaggerated peak exercise blood pressure (EBP) is associated with alteration of cardiometabolic risk factors and predict future resting hypertension (HT) in premenopausal women (paper 3). Final objective is to determine the influence of CRF and PA levels on cardiometabolic risk factors in non-obese women going through the menopause transition (paper 4).

## 2. LITERATURE REVIEW

### 2.1. Menopause

In life, women go through many biological transitions, starting from puberty through to the reproductive years until the cessation of ovarian function, known as menopause. During the reproductive years, women go through monthly cycles where ovaries secrete hormones such as estrogens (estrone, estrione, 17 $\beta$  estradiol) and progesterone which are controlled by the hypothalamopituitary-ovarian axis<sup>15,16</sup>. The hypothalamopituitary-ovarian axis is a closed loop negative and positive feedback system controlling the secretion of ovarian steroids and peptide hormones<sup>16</sup>. Estrogen is a hormone secreted throughout the menstrual cycle. Its surge is observed close to the ovulation phase and during the luteal phase, whereas progesterone is mostly secreted during the luteal phase<sup>15</sup>. During the reproductive years, women are considered premenopausal which is simply defined as the period preceding menopause<sup>17</sup>.

Perimenopause or menopause transition, is defined as the period around the onset of menopause that is often marked by women reporting various physical symptoms and/or signs such as menstrual irregularity/frequency and/or amenorrhoea for 3-11 months<sup>17,18</sup>. This is the period where estrogens seem to fluctuate uncontrollably with very high and very low levels, then start to decline gradually by late menopause transition until ovarian cessation<sup>19</sup>. Moreover, there is an increase in both the follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are at times associated with high or low levels of estrogens or simply the decrease in inhibin secretion<sup>16,19</sup>.

The last hormonal transition in a woman's life is the postmenopausal stage. Postmenopause is defined as the period that occurs after the final menstrual period whether it

was induced or spontaneous<sup>17</sup>. At this stage, the ovaries lack the capability of producing estrogens, especially estradiol, and can be identified by very high FSH levels<sup>19</sup>. It is important to note that androgens are still produced during this stage, however at lower quantity. Such decrease in estrogens and the presence of androgens have been shown to be associated with unfavorable body composition and metabolic changes that can lead to complications such as CVD<sup>20-22</sup>.

From a clinical point of view, menopause is defined as the permanent cessation of ovarian function and confirmed after 12 months of spontaneous amenorrhea<sup>23</sup>. The average age for menopause is approximately 51 years<sup>24</sup>. However, age tends to be lower in women who smoke, had an abdominal hysterectomy, earlier onset of menarche, or who are underweight/undernourished<sup>24</sup>. Physiologically, menopause occurs when ovarian follicle stores are depleted leading to decreased production of estrogens by the ovaries which is associated with increased FSH and LH levels<sup>24</sup>. Menopause is known to be a period associated with changes in body composition, such as a decrease in bone mineral density, lean body mass and an increase in fat mass, abdominal adiposity as well as an increased risk of cardiometabolic complications<sup>25-27</sup>. Estrogens deficiency has been suggested to be one of the underlying cause of these major cardiometabolic modifications which can lead to a rapid acceleration of CVD risks in women<sup>28</sup>. Estrogen is produced primarily by developing follicles in the ovaries and it functions as the primary female sex hormone. It promotes the development of female secondary sex characteristics, the proliferative phase of the menstrual cycle, oogenesis, ovulation, and the many physiological changes observed during pregnancy<sup>29,30</sup>. The major type and most abundant form of estrogen is 17 $\beta$ -estradiol; two other forms include estriol and estrone but are present at lower levels<sup>31</sup>. Normal estrogen

levels in females vary between 30-400 pg/ml during premenopause and 0-30 pg/ml after postmenopause.

## **2.2. Menopause and body composition**

### **2.2.1. Fat mass**

It is known that body weight, especially fat mass (FM), increases with aging in both men and women<sup>5</sup>. Nevertheless, such an increase becomes more prominent in women during and after the menopause transition, which suggests a potential influence of menopause on FM accumulation in postmenopausal women<sup>32</sup>. In fact, several studies have addressed the issue of weight change during menopause. Women gain on average about 0.45 kg of weight each year during the menopause transition, and gain as much as 5 kg of FM over 36 months in early postmenopause<sup>33,34</sup>. Sowers *et al.*<sup>35</sup> report findings from The Study of Women's Health Across the Nation (SWAN) that both chronological aging and ovarian aging contributed to a cumulative increase in FM of 3.4 kg and body mass index (BMI) of 1.2 kg/m<sup>2</sup> in a group of obese (BMI: 32.1 ± 8.1 kg/m<sup>2</sup>) premenopausal or early perimenopausal African-American and Caucasian women aged 42–52 years (n = 543) followed for 6 years. A different study reported that diet, PA, smoking habits, and BMI were still significantly higher among perimenopausal and postmenopausal women compared to premenopausal women<sup>36</sup>; an effect that persisted after adjusting for age. Another cross-sectional study by Toth *et al.*<sup>37</sup> looked at 53 premenopausal women and 28 postmenopausal women aged 47 ± 3 years and 51 ± 4 years, respectively. They reported that total body FM was 28% higher and % body fat was 17% higher in the postmenopausal women compared to the premenopausal women. The increase in FM remained significant, even after adjusting for age.

Lack of estrogen in females was associated with an increase in body fat<sup>22</sup>. Estrogen plays many roles with respect to body fat regulation. Estrogen has been shown to directly affect adipose tissue and act centrally to alter food intake and energy expenditure<sup>38</sup>.

This direct inhibitory effect is thought to occur through the inhibition of adipose deposition by decreasing lipogenesis due to a decrease of lipoprotein lipase (LPL) activity<sup>38</sup>. Estrogen can also affect adipogenesis by increasing proliferation and inhibiting differentiation of adipocytes<sup>39</sup>. The central effects of estrogen on FM has been associated with a reduction in food consumption, leptin secretion and an increase in energy expenditure<sup>38</sup>. Altogether, the presence of estrogen could help maintain or reduce fat deposition in females.

#### 2.2.2. Abdominal fat

An increase in abdominal obesity, especially visceral fat (VF) area ( $>110 \text{ cm}^2$ ), is associated with an exponential elevation of plasma triglycerides (TG), blood pressure (BP), plasma glucose concentration, insulin resistance and a reduction of high-density lipoprotein cholesterol (HDL-C)<sup>40,41</sup>. Therefore, visceral obesity is considered to play a major role in the development of the metabolic syndrome and CVD<sup>42,43</sup>.

Postmenopausal women are more prone to central obesity than premenopausal and perimenopausal women an effect attributed to altered estrogen secretion. It has been observed that postmenopausal women with obesity have significantly higher waist circumference (WC), waist-to-hip ratio (WHR) and VF compared to premenopausal women matched for BMI<sup>44</sup>. Longitudinal studies have also reported that women followed throughout

the menopause transition will show a progressive change in abdominal fat distribution with an increase in VF<sup>21,22,26,45</sup>.

It is suggested that perimenopause compared with early postmenopause status, is associated with significant changes in adipose tissue metabolism in both abdominal and gluteal fat depots<sup>46</sup>. In addition, estrogen plays an important role in body fat distribution. Estrogen-deficient postmenopausal women tend to accumulate more abdominal, especially VF, whereas premenopausal women have a more favorable fat distribution and accumulate more gluteo-femoral fat and abdominal subcutaneous fat (AScF)<sup>46</sup>. A possible explanation for such differences in body fat distribution is the decrease in LPL activity in femoral and abdominal subcutaneous adipocytes combined with a loss of lipolytic activity in visceral adipocytes<sup>47</sup>. Another possible explanation is through the activation of estrogen receptors (ER $\alpha$ ), where they up-regulate  $\alpha$ 2A-adrenergic receptors (anti-lipolytic) in subcutaneous and femoral fat, favouring fat deposition in these areas without having any effects on VF, maintaining high lipolytic activity<sup>48</sup>.

### 2.2.3. Lean body mass

Aging is associated with changes in body composition, and it has been noted that both men and women lose muscle mass as they age<sup>17</sup>. However, women going through the menopause transition can lose muscle mass and strength at a much faster rate compared to men<sup>49</sup>. An abnormally high loss in lean body mass which may be seen with aging in some women is called sarcopenia. Clinically, sarcopenia is defined as 2 standard deviations below the mean appendicular muscle mass of young healthy adults of a reference population<sup>50</sup>. A cross-sectional study by Rolland *et al.*<sup>51</sup> showed a decline of 0.6% and 1.17% in muscle

mass and muscle strength, respectively, in healthy postmenopausal women ( $54.1 \pm 4.3$  years). Moreover, a 6-year longitudinal study (SWAN) reported that there was an absolute cumulative decrease in skeletal muscle mass of approximately 0.23 kg (1.06%), which represents a yearly average decrease of 0.18% in a group of obese (BMI:  $32.1 \pm 8.1 \text{ kg/m}^2$ ) premenopausal or early perimenopausal African-American and Caucasian women<sup>35</sup>. When examining how menopause can affect lean body mass in women, it is believed that estrogen plays a role. There is evidence that estrogen receptors (ER) are present in skeletal muscles, under the form of ER $\alpha$  and ER $\beta$ <sup>49,50,52</sup>. With the presence of these receptors, it is somewhat expected that muscles should be responsive to estrogen. A recent study hypothesized that a decrease in estrogen concentration due to ovariectomy or menopause would result in changes in ER content<sup>49</sup>. Estrogen deficient mice have shown an increase in ER, especially ER $\alpha$ , as it is the most responsive to plasma levels of estrogens<sup>53</sup>. This suggests that muscles are estrogen responsive tissues. However, a comprehensive understanding of the physiological mechanisms underlying these changes remains to be elucidated. Yet again, it was hypothesized that as estrogen binds to its ER $\alpha$  there is an increase in antioxidant protein, such as superoxide dismutases and glutathione peroxidase, which in turn reduces oxidative stress, further improving muscle contractility and strength<sup>49</sup>. Other evidence has shown that estrogen can act as an antioxidant or as a membrane stabilizer influencing muscle membrane stability and reducing muscle damage by limiting membrane disruption and inflammation<sup>31</sup>.

## 2.3. Menopause and metabolic profile

### 2.3.1. Lipid profile

Dyslipidemia is a disorder characterized when one or more fasting plasma lipid concentrations meet the following criteria: TG  $\geq$  1.7 mmol/l, low-density lipoprotein cholesterol (LDL-C)  $\geq$  3.5 mmol/l, total cholesterol (TC)  $\geq$  5.0 mmol/l and HDL-C  $\leq$  1.3 mmol/l for women<sup>54</sup>. Dyslipidemia is a primary risk factor for CVD<sup>55</sup>. It was reported that both TG and HDL-C plasma levels are strong predictors of CVD among women<sup>56</sup>. Women in the highest quintile of TG had a 2.45-fold greater risk of CVD mortality than women in the lowest quintile, and the risk was increased to 3.81-fold with low HDL-C plasma levels<sup>57</sup>. It was found that plasma levels of TC, after menses have ceased, increased according to several studies<sup>58-60</sup>. A study comparing pre- and postmenopausal women of same age, BMI and WHR demonstrated that postmenopausal women had a 10%, 14% and 8.2% increase in TC, LDL-C and apolipoprotein (apo) B, respectively<sup>25</sup>. In that same study, no differences were found in blood glucose, insulin, TG, HDL-C, apoA1, and systolic and diastolic BP. It was concluded that TC, LDL-C and apoB are the primary CVD risk factors affected by menopause. Longitudinal studies have also shown increased blood lipid profile risk in women going through the menopause transition<sup>27,61-64</sup>. Variations in lipid profile have been noted across the menopause transition showing an increase TC (6%), TG (11%) and LDL-C (10%) concentrations as HDL-C concentrations virtually remained unchanged<sup>62</sup>. Derby *et al.*<sup>61</sup>, based on the results of the SWAN study, also showed changes in the lipid profile. They specifically noted that alterations in TC, TG, LDL-C and HDL-C concentrations seemed to peak around the late perimenopause or early postmenopause stages, suggesting that these

changes occur during the menopause transition, especially during the late menopause transition.

One plausible explanation to justify an independent role of menopause on the changes in plasma lipid profile is thought to be related to the hormonal modification associated with menopause<sup>65</sup>. Low level of circulating estrogen was found to be linked to high TC, TG, LDL-C and/or low HDL-C plasma levels<sup>65</sup>. In fact, the intra-hepatic action of estrogen increases the catabolism and clearance of LDL-C by increasing the number of apoB receptors in the liver, while doing the opposite for HDL-C<sup>66</sup>. Estrogen also promotes the biliary secretion of cholesterol, the esterification of cholesterol and increases the clearance of chylomicrons<sup>66</sup>, reducing the accumulation of cholesterol in systemic circulation and body tissues.

Another plausible explanation for the changes in lipid profile is through the increase in body FM or more specifically abdominal VF. Obesity which is defined as an excess of weight, especially an excess of body FM, is associated with an increased risk of insulin resistance, T2D and CVD<sup>67,68</sup>. Studies have shown that % fat is a predictor of cardiovascular risk factors<sup>69,70</sup>. As reported in a previous study, % fat was found to be a strong independent factor related to elevated systolic and diastolic blood pressure, TG, LDL-C, and LDL-C/HDL-C ratio and a reduced HDL-C concentrations, altogether increasing the risk of CVD<sup>70</sup>.

### 2.3.2. Glucose – Insulin

Impaired glucose tolerance and insulin resistance are both risk factors that can lead to T2D, the metabolic syndrome and then CVD in individuals<sup>71,72</sup>. T2D is associated with 2 – 4

fold higher risk of CVD, and up to 3 fold higher risk of all-cause mortality compared to men and women without diabetes<sup>72</sup>. The most likely cause of impaired glucose and insulin resistance is an excess of total body fat, especially abdominal VF<sup>73</sup>. Abdominal obesity is thought to be related to increased insulin resistance, hyperinsulinemia and increased risk of T2D independent of total body fat<sup>73</sup>. The mechanism leading to such disturbance has been fully reported. It has been shown that an increased accumulation of VF is associated with an increased flow of free fatty acids in the portal vein, which results in lipid accumulation in the liver, decreased insulin sensitivity and an increased insulin disposal rate by the liver. Moreover, this promotes the synthesis and excretion of glucose and TG by the liver<sup>74,75</sup> and can further promote the development of features of the metabolic syndrome<sup>76</sup>.

Whether menopause *per se* is associated with increased insulin resistance or impaired glucose, is not clear in the scientific literature. It was shown that fasting plasma levels of insulin and glucose are higher in postmenopausal women compared to premenopausal women, suggesting that menopause is associated with insulin resistance<sup>77</sup>. For instance, Wu *et al.*<sup>78</sup> reported data from 5412 women and suggested that an increase in the number of years since menopause has a negative impact on glucose tolerance with an increased risk of impaired glucose tolerance of 6% per year after menopause. However, others did not show such an association or effect of the menopause transition on insulin resistance or impaired glucose<sup>22,63</sup>. Guthrie *et al.*<sup>71</sup> reported data on 110 premenopausal, 138 perimenopausal and 17 postmenopausal women (age:  $46 \pm 57$  years) followed for 5 years in the longitudinal study of Melbourne Women's Midlife Health Project. During the study period, 16% of women developed impaired fasting glucose ( $\geq 6.1$  mmol/l), and this impairment was found to be more related with total body FM and dyslipidemia at baseline and not to the

menopause transition *per se*. Thus, the literature on this topic is sparse and an area ripe for scientific inquiry.

#### **2.4. Menopause symptoms**

As women go through the menopause transition, many experience menopausal symptoms where frequency and severity can vary from one woman to another<sup>17</sup>. The more common symptoms that are found to be related to the menopause transition are:

- 1) Vasomotor symptoms (hot flashes and night sweats)
- 2) Sleep disturbance / Insomnia
- 3) Mood changes / psychological symptoms
- 4) Sexual dysfunction
- 5) Impaired concentration and memory
- 6) Urogenital symptoms.

VMS are thought to be the most common symptoms in women with irregular periods or menopausal women<sup>17</sup>. VMS are sensations of intense heat (i.e., hot flashes) accompanied by sweating. VMS are associated with a poor quality of life and sleep, poor memory performance, and mood changes<sup>79</sup>. However, it is worth mentioning that such symptoms may start as early as 5 to 10 years before menopause and may even occur 10 years after menopause<sup>80</sup>. One cross-sectional study reported on the severity of VMS complaints in 5213 women between the ages of 39 and 60 years<sup>81</sup>. In this study, it was noted that 41% of women aged 39 years and up with a regular cycle complained of VMS. Around the onset of menopause, it affected 85% of women and then slowly declined to reach 57% after 10 years or more in postmenopausal women. Furthermore, severe VMS were present in 3% of women

with a regular cycle, in 30% of women nearing the onset of menopause, and in 7% of postmenopausal women after 10 years. Although the causes of these symptoms are not fully known, it was suggested that they may be triggered by small elevations in body temperature, acting on a reduced thermoneutral zone<sup>82</sup>. Hot flashes are thought to result from the brain's response, in part, to diminished hormones and hormonal fluctuations that occur during the menopause transition, and an elevated sympathetic activity (norepinephrine). This could lead to the narrowing of the thermoneutral zone and instability of the thermoregulatory mechanisms that regulate temperature homeostasis in the hypothalamus<sup>82</sup>.

Other than lack of estrogen, early onset of menopause and/or long perimenopausal phase are risk factors for more frequent and intense VMS<sup>83</sup>. Other risk factors for increased VMS are high BMI and smoking. A BMI  $\geq 25.0$  kg/m<sup>2</sup> has been associated with an increased frequency of daily hot flashes; however, such an association was observed only among pre- and perimenopausal women<sup>83</sup>. Another study found that out of 274 postmenopausal women (age:  $54.5 \pm 5.3$  years), only those with a BMI  $\geq 25.0$  kg/m<sup>2</sup> and android fat distribution had a poor health-related quality of life and experienced more menopausal symptoms<sup>84</sup>. Furthermore, in the SWAN study, the authors aimed to examine whether body fat gain, measured by bioelectrical impedance, was associated with the presence of VMS over time in 1659 women between the ages of 47-59 years followed for 4 years<sup>79</sup>. They found that body fat gain, adjusted for age, geographical region, race/ethnicity, education, smoking, parity, anxiety, and menopausal status, was associated with greater odds of reporting hot flashes (odds ratio = 1.23, 95% confidence interval (CI): P = 0.03).

Among menopausal women, those experiencing VMS were found to have an increased risk of presenting cardiometabolic risk factors. Gast *et al.*<sup>85</sup> previously reported that women

(N= 5648; age: 46-57 years) with VMS had a higher BMI, plasma TC and systolic and diastolic BP. In a separate investigation by the same research group, women (N= 5857; age: 50-64 years) with VMS had a higher waist-to-hip ratio, plasma glucose level, LDL-C and TG concentrations compared to women without VMS<sup>86</sup>. On the other hand, one study in particular reported that an unfavourable cardiometabolic risk profile (TC, HDL-C, BP, T2D and smoking) was not associated with VMS in a group of pre- peri- and postmenopausal women between the ages of 50-70 years<sup>87</sup>. Furthermore, a recent study by Gast *et al.*<sup>88</sup> examined whether VMS were related to a future risk of CVD in women (N= 10787; age: 53.6±4.1 years) combining data of two cohorts: The Eindhoven Perimenopausal Osteoporosis Study<sup>89</sup> and The Women's Health in the Lund Area (WHILA) Study<sup>90</sup>. In women followed for 10 years they found that hot flashes were not significantly associated with an increase in CVD risk, but the presence of night sweat was associated with a hazard ratio of 1.33 (95% CI, 1.05-1.69) for CVD. This association was attenuated, but not eliminated, after adjusting for BMI, BP and TC (hazard ratio, 1.25; 95% CI, 0.99-1.58). Furthermore, Szmulowicz *et al.*<sup>91</sup> reported that women experiencing late VMS, defined as VMS at menopause onset, were at an increased risk of CVD and all-cause mortality, whereas women with early VMS, defined as VMS at enrollment of the study, did not present an increased risk of CVD. In fact, their average risk was reduced compared to the average risk of women with late VMS.

Replacement hormone therapy (RHT) is useful in reducing VMS in women. Conversely, RHT may have possible adverse effects such as increasing the risk of coronary heart disease, stroke, thromboembolic events, breast cancer with 5 or more years of use and cholecystitis<sup>80,92</sup>. On the other hand, lifestyle changes such as an increase in PA may be a

viable alternative, yet scientific evidence in this area is inconclusive. Associations between VMS and PA have been demonstrated in both cross-sectional<sup>93,94</sup> and longitudinal<sup>95,96</sup> studies, yet other studies did not find any relationship between PA and VMS<sup>80,97</sup>. In fact, the Australian Longitudinal Study on Women's Health<sup>80</sup> showed that the change in weight had a stronger association with the prevalence of VMS than PA.

## 2.5. Blood pressure

Blood pressure (BP) measures the force exerted by the blood on the arteries; it is expressed by two values: 1) systolic BP, the highest pressure, reflects the pressure on the arterial wall during a systole; 2) diastolic BP, the lowest pressure, reflects the pressure on the arterial wall during a diastole<sup>98</sup>. Normal BP at rest is defined as a value less than 120 mmHg systolic and 80 mmHg diastolic. The different classifications of BP are presented in Table 1 according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>99</sup>.

Table 1. Blood pressures classification in adults.

	Blood pressure (mmHg)	
	systolic	diastolic
Normal	< 120	< 80
Prehypertensive	120-139	80-89
Hypertension		
Stage 1	140-159	90-99
Stage 2	≥ 160	≥ 100

Source: adapted from the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>99</sup>

Hypertension (HT), also known as "high blood pressure", is a condition in which the arteries constantly carry blood at high pressure<sup>100</sup>. In fact, HT is one of the major risk factors

for CVD. This condition may also cause renal and arterial impairment, as well as weaken body organs<sup>101</sup>. Despite the fact that HT can be prevented by a healthy lifestyle such as a healthy diet and regular PA, approximately 19% of Canadians over the age of 20 years suffer from this condition<sup>102</sup> and 18.4% of Canadians between the ages of 40 to 59 have high BP<sup>102</sup>. However, it is important to note that in general the prevalence of the HT is underestimated because of the absence of symptoms in the majority of individuals<sup>103,104</sup>. The exact causes of HT are not identified, but several factors appear to be highly correlated with this condition, including, age, family history of HT, smoking, obesity, diabetes, sedentary lifestyle, high sodium (> 1.5 g daily) intake, high alcohol consumption and stress<sup>101</sup>. Menopause may be another factor associated with higher BP. It was found that premenopausal women have lower BP compared to postmenopausal women<sup>105</sup>. It was also reported that increases in BP were greater during the postmenopausal stage than the perimenopausal stage<sup>106</sup>. More specifically, it was demonstrated in a cross-sectional study that the average increase in BP in postmenopausal women depends on the age at menopause and the time spent in the postmenopausal period. This suggests that a longer estrogen deficiency may be the culprit to higher BP in women<sup>105</sup> because of a decline in endothelium dependent vasodilation<sup>107</sup>. On the other hand, longitudinal studies have shown that the changes in systolic and diastolic BP were related to aging and not menopausal status<sup>63,108</sup>.

During an acute bout of dynamic exercise, BP increases linearly with cardiac output, oxygen consumption, and work load<sup>30</sup>. Specifically, systolic BP increases while diastolic BP remains unchanged or decreases slightly. A normal systolic BP response to acute exercise is approximately  $10 \pm 2$  mmHg per metabolic equivalent (MET) and may reach a plateau at peak exercise<sup>109</sup>. However in some individuals, BP response during exercise testing

abnormally rises. Such a condition is known as an exaggerated peak exercise blood pressure (peak EBP), which is defined as an abnormally elevated systolic (S) and/or diastolic (D) BP response during exercise testing in individuals with a normal resting BP<sup>110</sup>. Exaggerated peak EBP response is diagnosed when peak ESBP is  $\geq 190$  and/or peak EDBP  $\geq 105$  mmHg in women and peak ESBP  $\geq 210$  and/or peak EDBP  $\geq 105$  mmHg in men<sup>111,112</sup>. While these values were determined based on the data from the general population of the Framingham study<sup>111-113</sup>, other studies have specifically used different criteria for exaggerated peak ESBP in men:  $\geq 200$  mmHg<sup>110,114</sup>,  $\geq 220$  mmHg<sup>115</sup>, and  $\geq 230$  mmHg<sup>116</sup>. Overall, this phenotype has been suggested to be a risk factor for future development of HT at rest in asymptomatic individuals<sup>113,114</sup>. Studies in men have shown that within a 5-year follow-up at least 33% of patients with an exaggerated peak ESBP response developed resting HT, compared to men with a normal peak ESBP<sup>114,116</sup>. Furthermore, specific characteristics have been found to be associated with such phenotype, the most common are high values of resting systolic and diastolic BP<sup>110,115</sup>, BMI<sup>117,118</sup>, WC<sup>118</sup>, fasting blood glucose concentration<sup>115,118</sup>, insulin resistance<sup>115,118</sup> and abnormal plasma lipid profile<sup>119,120</sup>. These factors may be the reason behind such exaggerated response in BP during exercise. Nonetheless, other factors have been associated with an exaggerated peak EBP such as increased sympathetic vasoconstriction, a diminished blood nitric oxide concentration in the vasculature which may in turn increases arterial stiffness in the long run<sup>109,121</sup>. All together, this leads to an increased heart rate, cardiac contractility and cardiac output and consequently leads to a chronically increased BP<sup>115,122</sup>.

## 2.6. Physical activity energy expenditure

Energy expenditure (EE) is defined as the total consumption of energy by all activities done by the body, both involuntary and voluntary<sup>123</sup>. Humans oxidize carbohydrate, protein and fat to produce energy. This energy is important to maintain general body functions, body temperature as well as physical activity (muscle contraction)<sup>123</sup>. The average daily EE of an adult individual engaged in normal PA can range from 1800 to 3000 kcal<sup>124</sup>. On average, in healthy adults, about 70% of the daily EE is represented by resting metabolic rate (RMR), 10 to 15% is due to thermal effect of food and 15 to 20% is related to physical activity<sup>125</sup>.

### 2.6.1. Physical activity

Physical activity is defined as a form of leisure and non-leisure body movement produced by the skeletal muscles<sup>10</sup>. According to the Canadian physical activity guidelines<sup>126</sup>, adults are recommended to accumulate at least 150 minutes of moderate to vigorous intensity aerobic PA per week in bouts of 10 minutes or more. They also recommend doing muscle and bone strengthening activities at least 2 days per week.

It is currently unknown whether the change from pre- to postmenopausal status has an independent effect on the decrease in PA. In rats, it was found that wheel running time was reduced after surgical ovariectomy and was increased after hormones were reintroduced<sup>127</sup>. The increase in PA is thought to be caused by the activation of the estrogen receptors which leads to the regulation of certain physiological structures such as the alteration in dopaminergic systems as well as possible non-genomic actions of estrogen<sup>127</sup>. Collectively, this suggests that menopause *per se* can directly contribute to the decrease in PA. However, this is not always obvious in humans. Some studies reported that women going through the

menopause transition presented some functional limitations such as walking or climbing the stairs, deterioration in muscle strength and other various activities, thereby reducing their PA<sup>128,129</sup>. Yet again, both of these studies are cross-sectional and can neither show whether the limitation is progressive nor show further progress in women after the menopause transition. Additionally, they did not control for age in their analysis, knowing that age is also associated with a decrease in PA<sup>124</sup>. The longitudinal study performed by Lovejoy *et al.*<sup>22</sup> reported that PA dropped by more than 30% with time on average in both pre and postmenopausal women, showing no significant difference between groups (% change: -38.7% for premenopausal women vs. -30.2% for postmenopausal women). Therefore, they did not observe an independent effect of menopause *per se* on physical activity EE.

Regular PA is an optimal strategy to reduce the risk of CVD<sup>130</sup>, improve body composition<sup>131</sup>, normalize blood lipid profile and blood pressure<sup>132</sup>, as well as certain inflammatory markers such as c-reactive protein<sup>133,134</sup> in women. Hu *et al.*<sup>135</sup> demonstrated a lower risk of mortality from CVD in active women with obesity and an even lower risk in non-obese active women compared to their counterparts who were physically inactive. A strong relation has been established between BMI, FM and PA, and exercise has been shown to have a strong independent inverse effect on BMI and FM<sup>135-137</sup>. It is also clear that physically active people have less abdominal fat, compared to sedentary people<sup>138</sup>. It was reported that PA levels were negatively and significantly correlated with VF accumulation<sup>139</sup>.

Many studies have confirmed that regular PA attenuates the accumulation of VF and the associated CVD risk in women<sup>140-142</sup>. Also, studies have found that light-to-moderate<sup>8</sup> or high-intensity<sup>143</sup> exercises are associated with a lower CVD rate in women. It was noted that

women who are active during the adulthood years are more likely to be active when older, thus predicting a lower risk of CVD<sup>144</sup>. Another study found that the relative risks of death from any cause and CVD among participants with multiple risk factors (hypertension, chronic obstructive pulmonary disease, diabetes, smoking, BMI  $\geq 30.0$  kg/m<sup>2</sup>, and high TC  $\geq 5.70$  mmol/L) are lower in those who reported achieving exercise more than 5 METs (metabolic equivalents) during adulthood than those who reported less than 5 METs of exercise per day<sup>145</sup>. A 5-year study on the Women's Health Lifestyle Project reported that women who underwent a lifestyle program of PA (1000-1500 kcal/week) and a diet plan (reduce fat intake by 25%) showed a reduction in the rise of cardiometabolic risk factors and body weight when compared to women in the control group<sup>146</sup>. Furthermore, some studies have shown that physical activity levels are associated with lower blood concentrations of inflammatory markers<sup>133,134</sup>. Mora *et al.*<sup>134</sup> reported that a modest level of PA (at least 1000 kcal/wk or 2.5 hr/wk) is significantly associated with more favorable level of CRP, Apo A1, fibrinogen, ICAM-1 in 27158 healthy women (age =  $54.7 \pm 7.1$ ; BMI =  $25.9 \pm 5.0$  kg/m<sup>2</sup>) compared to lower levels of PA.

When it comes to menopause, PA seems to have beneficial effects on body composition and blood lipid profile. A study by Sternfeld *et al.*<sup>147</sup> has noted that late peri- and postmenopausal women who engaged in higher level of PA showed significantly lower % body fat and WC than women who engaged in moderate PA. It was thus suggested that regular PA may help reduce the risk of weight gain and prevent the negative changes in body composition and abdominal fat accumulation observed during the menopausal transition. A prospective study reported that after a 12-week weight reduction program, including 21 premenopausal and 19 postmenopausal obese women, postmenopausal women lost on

average less VF compared to the premenopausal group<sup>148</sup>. One possible reason for this outcome is that VF could be more sensitive to changes during weight reduction in premenopausal women because of the presence of circulating sex hormones, which are deficient in postmenopausal women. Another reason could simply be that postmenopausal women had more VF to start with, compared to premenopausal women, but that was not significantly different<sup>148</sup>. As previously mentioned, VF accumulation during menopause increases the risk of metabolic abnormalities and CVD, yet PA seems to attenuate this effect<sup>149</sup>. Furthermore, Hagner *et al.*<sup>150</sup> reported that a 12-week moderate intensity Nordic Walking program decreased average BMI, body FM, plasma LDL-C, TG, TC concentrations and WC, while increasing plasma HDL-C concentration and VO<sub>2</sub> max in a group of premenopausal (N = 65; age = 36.5 ± 5.2 years; BMI = 31.5 ± 5.4 kg/m<sup>2</sup>), perimenopausal (N = 53; age = 49.3 ± 2.9 years; BMI = 31.7 ± 5.1 kg/m<sup>2</sup>) and postmenopausal (N = 53; age = 62.5 ± 5.4 years; BMI = 31.1 ± 4.6 kg/m<sup>2</sup>) women. Significant differences were observed between the menopausal status groups for all variables, both before and after the exercise intervention program, with the exception of fasting plasma TG concentration and WC. Overall, the premenopausal group presented with a healthier and more favorable body composition and cardiometabolic profile, followed by the perimenopausal and postmenopausal groups.

## **2.7. Cardiorespiratory fitness**

### **2.7.1. Cardiovascular disease**

It is important to specify that cardiorespiratory fitness (CRF), as defined by maximal oxygen consumption (VO<sub>2</sub> max or VO<sub>2</sub> peak) measurements during an exercise test, is

another independent risk factor of CVD. A decline in CRF is associated with an increased risk of CVD, particularly coronary heart disease (CHD)<sup>151</sup>, partly due to an increased incidence of obesity, hypertension, and type 2 diabetes<sup>152</sup>. A study performed by Dvorak *et al.*<sup>153</sup> in 53 men ( $68 \pm 6.9$  yrs) and 63 women ( $67 \pm 6.7$  yrs) found that high levels of CRF ( $>27.7$  ml·kg<sup>-1</sup>·min<sup>-1</sup> for men and  $>21.7$  ml·kg<sup>-1</sup>·min<sup>-1</sup> for women) have greater cardioprotective effects than high levels of PA *per se*. In healthy women, menopause is associated with cardiopulmonary modifications (or alterations) caused by estrogen deficiency and a reduced level of nitric oxide in the vasculature. These modifications account partially for the impairment of endothelium-dependent vasodilation, preventing O<sub>2</sub> flow through the vasculature that is required to match the increased O<sub>2</sub> requirement during exercise<sup>154</sup>. Lynch *et al.*<sup>77</sup> demonstrated that postmenopausal women have on average lower (-17%) VO<sub>2</sub> max compared to premenopausal and perimenopausal women of similar age and adiposity, suggesting that they are at a higher risk of CVD.

The recommended guidelines of exercise prescription to maintain CRF and body composition according to the American College of Sport Medicine (ACSM) for healthy adults are as followed<sup>155</sup>:

1. Frequency: 3-5 days/week, preferably every day.
2. Intensity: 40/50%-85% of maximum oxygen uptake reserve (VO<sub>2</sub> R) or heart rate reserve (HRR), or 64%/70% to 94% of maximum heart rate (HR max).
3. Duration: 20-60 min of continuous or intermittent (minimum of 10-min bouts accumulated throughout the day) aerobic exercise.
4. Mode: any type of activity that uses large muscle groups, e.g., walking-hiking, running-jogging, cycling-bicycling, cross-country skiing, aerobic dance/group exercise, rope skipping, rowing, stair climbing, swimming and skating.

### 2.7.2. Cardiometabolic risk factors

Low CRF is associated with an increase risk of obesity<sup>140</sup>. Further results confirm that CRF is significantly decreased in women with obesity compared to lean women, and  $\text{VO}_2$  per kilogram fat-free mass for both groups is negatively and moderately related to BMI ( $r = -0.37$ ) and % body fat ( $r = -0.40$ )<sup>156</sup>. In 44 obese, sedentary, postmenopausal women, an increase in PA and CRF was linked with an average reduction in body weight (26.5%), FM (27.4%) and % body fat (22.4%) after a 6-month lifestyle change intervention<sup>157</sup>. A study performed by Ross, *et al.*<sup>158</sup> in premenopausal women with abdominal obesity, reported that VF alone was strongly correlated with insulin resistance independent of AS<sub>CF</sub>, muscle adipose tissue and CRF. A decrease in CRF has been shown to be associated with an increase in VF, which leads to a cluster of cardiometabolic disturbances and CVD (Figure 1) in individuals<sup>159</sup>. High CRF  $\geq 43.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (men) and  $\geq 33.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (women) were associated with a significant reduction in total and abdominal obesity compared to low CRF  $< 38.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (men) and  $< 29.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (women) for a given BMI<sup>160</sup>. Lynch *et al.*<sup>161</sup> performed a study that aimed to determine whether the loss of VF is related to improvements in CRF, following a weight loss program and walking intervention in postmenopausal women. The intervention resulted in a significant reduction in body weight, total FM, VF, and AS<sub>CF</sub> area with no significant change in lean body mass. The reduction in VF was negatively correlated with the improvement of CRF ( $r = -0.47$ ) and 30% of the inter-individual change in VF was explained by a change in  $\text{VO}_2$  max and FM. Women who increased their CRF by 10% presented a 20% reduction in VF area compared to those who did not increase their CRF.

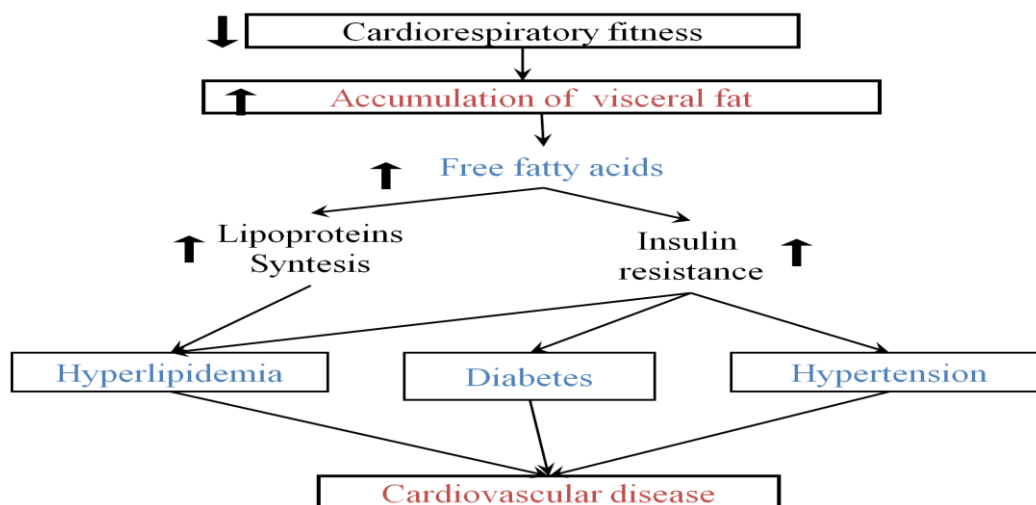


Figure 1. Potential mechanism of certain diseases related to a low cardiorespiratory fitness and visceral obesity. Source: adapted from Matsuzawa, Y. *et al.*<sup>159</sup>.

Higher level of CRF was significantly associated with plasma TC ( $r = -0.32$ ), TC/HDL-C ( $r = -0.35$ ), TG ( $r = -0.32$ ), and HDL-C ( $r = 0.18$ ) concentrations in 283 non-smoking, non-obese (age =  $53.0 \pm 7.1$  years; BMI =  $23.2 \pm 4.0$  kg/m<sup>2</sup>) postmenopausal women<sup>162</sup>. In that study, the authors concluded that CRF was an important independent determinant of blood lipids in postmenopausal women. Regular PA and improvement in CRF has been shown to increase HDL-C and decrease TG plasma levels in adults<sup>163</sup>. In women, inverse associations were found for plasma TG and TC/HDL-C ratio, and a positive association for HDL-C with CRF<sup>164</sup>. Also, it was shown that cardiorespiratory fitness is inversely associated with inflammatory marker levels in the general population<sup>165</sup>. For example in a study by LaMonte *et al.*<sup>166</sup>, plasma CRP levels were lower in higher tertiles of cardiorespiratory fitness in 135 overweight women (age =  $55.0 \pm 11.0$  year) with unknown menopause status. In another study by Giallauria *et al.*<sup>167</sup> in 124 premenopausal women with polycystic ovary syndrome, cardiorespiratory fitness was inversely associated with plasma CRP as well as fibrinogen concentrations. Furthermore, women who are overweight or obese with a high level of CRF have been shown to have higher insulin sensitivity than sedentary individuals with obesity

and low CRF<sup>168</sup>. These results may partially explain why the risk of CVD mortality increases across the continuum from fit women with obesity, lean unfit women, to unfit women with obesity, compared to lean and fit women<sup>169</sup>.

## CHAPTER 2

### 1. SPECIFIC PROBLEM

Throughout the literature review, we have noted that the menopause transition is a critical period in a woman's life that seems to have various bio-psycho-social effects on women. The major changes associated with menopause transition, besides VMS, are changes in body composition, body fat distribution, cardiometabolic risk profile, level of PA and CRF<sup>4</sup>. However, the presence and the level of these changes vary among individuals as well as the associated risk of CVD based on the woman's menopausal status and the presence or absence of VMS<sup>5,85</sup>.

Both cross-sectional and longitudinal studies have reported that menopause transition is associated with changes in body composition and cardiometabolic profile in overweight or obese women<sup>20,22,35,63,170-172</sup>. On the other hand, cross-sectional studies<sup>36,173-182</sup> do not allow for causal conclusions to be made (i.e., to assess cause-and-effect relationships) and none of the longitudinal studies<sup>20,22,35,170,172</sup> published to date provide direct measures of both body composition and body fat distribution change in healthy non-obese (BMI < 30.0 kg/m<sup>2</sup>) women undergoing the menopause transition.

Furthermore, menopausal symptoms, more specifically VMS, have been associated with increased risk of CVD and all-cause mortality. Women with a high BMI or FM were the ones presenting the most symptoms compared to normal weight women<sup>79</sup>. However, the majority of studies included women with a wide range of BMI and % body fat<sup>79,86,183-185</sup> from multi-ethnic population<sup>79,91,184-186</sup> and have mostly used a cross-sectional study design<sup>4, 8-10, 12</sup>. Also, a small number of studies used bioelectric impedance to estimate body

composition (e.g. fat mass and lean body mass)<sup>79,185,187</sup>, while the majority did not use a gold standard method to measure body composition and body fat distribution<sup>86,91,183,184,186,188</sup>.

Most studies that investigated the exaggerated peak EBP in association with cardiometabolic risk factors were cross-sectional<sup>110,113,115,117-120,189</sup> and included either only men<sup>114,115,117,119</sup> or consisted mostly of men<sup>110,113,118,120</sup>. None of the studies appear to have included non-obese premenopausal women and followed them through the menopause transition.

High CRF and PA, on the other hand, have been shown to reduce cardiometabolic risk factors and to improve overall quality of life. However, longitudinal studies of the effects of menopause transition on PA and CRF are lacking, therefore a study exploring this matter is warranted. The evidence supporting a relationship between CRF and/or PA levels and CVD risk factors has been well documented in the general population. Still, it is questionable if these relationships are the same in women going through the menopause transition, a period in a woman's life that is associated with hormonal changes, especially a progressive decrease in estrogen<sup>22</sup>, which is associated with an increase incidence and prevalence of cardiometabolic risk factors<sup>22</sup> and CVD<sup>34</sup>.

## 2. OBJECTIVES & HYPOTHESES

**First:** To examine changes in body composition and cardiometabolic risk factors in non-obese women going through the menopause transition (MONET Group Study). Our first hypothesis was that women who will have become postmenopausal at the end of the study will show increases in weight, total FM and VF. Our second hypothesis was that women who will display increased VF after the follow-up will also present a greater deterioration in their cardiometabolic profile.

**Second:** To compare body composition, body fat distribution, and cardiometabolic risk factors in non-obese premenopausal women with and without VMS. To determine the influence of PA levels and intensity on the prevalence of VMS throughout the menopause transition (MONET Group Study). We tested the following hypothesis: women experiencing VMS during menopausal transition, specifically hot flashes and/or night sweats, would show higher levels of adiposity, and cardiometabolic risk factors. Also, high PA levels would be associated with a lower prevalence of VMS.

**Third:** To investigate if an exaggerated peak EBP is associated with alteration of cardiometabolic risk factors and predict future resting HT in premenopausal women (MONET Group Study). We hypothesized that women with an exaggerated peak EBP response would 1) have higher resting SBP and DBP, adiposity and cardiometabolic risk factors; 2) predict future resting HT in healthy normotensive middle-age women in transition to menopause.

**Fourth:** To determine the influence of CRF and PA levels on cardiometabolic risk factors in non-obese women going through the menopause transition (MONET Group Study). We tested the following hypothesis: CRF and physical activity levels would be related with a favourable cardiometabolic risk profile in women followed through the menopause transition.

## **CHAPTER 3**

### **1. METHODS**

Methods used in the present thesis are detailed within the methodology section of each article in chapters 4 to 8.

## CHAPTER 4

### **THE EFFECT OF MENOPAUSAL TRANSITION ON BODY COMPOSITION AND CARDIOMETABOLIC RISK FACTORS: A MONET GROUP STUDY**

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No permission letter is needed from Wolters Kluwer Health, Lippincott Williams & Wilkins (*Menopause*. 2012 Jul;19(7): 760-767)

#### Author contributions:

Éric Doucet, Martin Brochu, Jean-Marc Lavoie, Irene Strychar, Rémi Rabasa-Lhoret, Denis Prud'homme participated in the development of the research project (MONET). Joseph Abdunour participated in the data collection. Joseph Abdunour and Denis Prud'homme performed the analysis and interpretation and completed the writing of the manuscript. All authors were involved in the revision and interpretation of the paper.

## The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study

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### Abstract

**Objective:** Cardiovascular disease is the first cause of mortality in women in North America. The risk of cardiovascular disease increases sharply after middle age in women, especially after menopause. The aim was to investigate changes in body composition and cardiometabolic profile throughout the menopausal transition.

**Methods:** This was a 5-year observational, longitudinal study on the menopausal transition. The study included 102 premenopausal women at baseline (age,  $49.9 \pm 1.9$  y; body mass index,  $23.3 \pm 2.2$  kg/m<sup>2</sup>). Outcome measures include menopause status, body composition by dual-energy x-ray absorptiometry (total fat mass [FM], trunk FM, and total fat-free mass), waist circumference, visceral and abdominal subcutaneous fat, fasting glucose and insulin levels, homeostasis model assessment of insulin resistance, plasma lipid levels (triglycerides, total cholesterol, and high- and low-density lipoprotein cholesterol), and resting blood pressure.

**Results:** Repeated-measure analyses revealed significant increases for FM, percentage FM, trunk FM, visceral fat, plasma fasting glucose, and high-density lipoprotein cholesterol ( $0.05 > P < 0.01$ ) and a significant decrease for plasma glucose levels after follow-up. Those who were in perimenopause or postmenopause by year 3 of the study showed a significant increase in visceral fat ( $P < 0.01$ ) compared with baseline. Despite some significant changes in the metabolic profile among the menopause statuses, the women did not show any cardiometabolic deterioration by the end of the study.

**Conclusions:** Our results suggest that changes in body composition and fat distribution can occur in nonobese women as they go through the menopausal transition. However, these changes were not accompanied by cardiometabolic deteriorations in the present study.

**Key Words:** Menopause – Body composition – Cardiometabolic risk factors – Visceral fat.

Cardiovascular disease (CVD) is the leading cause of death in women in many developed countries, and this risk sharply increases after menopause.<sup>1</sup> Such an

increase in the incidence of CVD has been related to body composition and cardiometabolic changes that occur throughout the menopausal transition.<sup>2</sup> It has been reported that body mass index (BMI) was found to be significantly higher in perimenopausal and postmenopausal women compared with premenopausal women even after controlling for age, diet, physical activity levels, and smoking habits.<sup>2</sup> Both fat mass (FM) and waist circumference (WC) have also been shown to increase throughout the menopausal transition in a group of premenopausal and perimenopausal women after a 6-year follow-up.<sup>3</sup> It was also reported that postmenopausal women presented a lower abdominal subcutaneous fat (AScF)–to–visceral fat (VF) ratio compared with premenopausal women matched for age.<sup>4</sup> VF, in turn, is associated with metabolic complications such as insulin resistance (IR), dyslipidemia, type 2 diabetes, and metabolic syndrome.<sup>5,6</sup> Menopause has also been reported to be associated with a deleterious effect on plasma lipids, lipoproteins, and IR.<sup>7,8</sup> However, glucose homeostasis does not seem to be affected by menopause per se but more by the weight gain that occurs during menopause.<sup>7,9</sup>

Both cross-sectional and longitudinal studies have reported that menopause is associated with changes in body composition and metabolic profile in overweight or obese women.<sup>3,10-15</sup>

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However, cross-sectional studies<sup>2,4,16</sup> do not allow us to conclude that a cause-and-effect relationship exists or to detect changes observed in the population's characteristics compared with longitudinal studies. Furthermore, none of the longitudinal studies<sup>3,10-12,15</sup> published to date provide direct measures of both body composition and fat distribution change in a group of healthy nonobese (BMI, <30 kg/m<sup>2</sup>) women undergoing the menopausal transition.

The main objective of this study therefore was to examine changes in body composition and cardiometabolic risk factors in nonobese women going through the menopausal transition. Our first hypothesis was that women who will have become postmenopausal at the end of the study will show increases in total FM and VF. Our second hypothesis was that women who will display increased VF after the follow-up will also present a greater deterioration in their metabolic profile.

## METHODS

### Participants

The study included 102 healthy premenopausal women aged between 47 and 55 years participating in the Montreal-Ottawa New Emerging Team group study, which was a 5-year longitudinal study (2004 to 2009) on the effects of the menopausal transition on body composition and cardiometabolic risk factors. This age range was selected, so the women would most probably become postmenopausal by the end of the study. Participants were recruited using community advertising and referrals from the Ob/Gyn clinics. Figure 1 presents the recruitment diagram and sample size of the premenopausal women at baseline.

Premenopausal women were included if they met the following criteria: (1) premenopause status (two menstruations in the last 3 months, no increase in cycle irregularity in the

12 months before testing, and a plasma follicular-stimulating hormone level <30 IU/L as a mean of verification), (2) aged between 47 and 55 years, (3) no surgically induced menopause, (4) nonsmoker, (5) BMI between 20 and 29 kg/m<sup>2</sup>, and (6) reported weight stability ( $\pm 2$  kg) for 6 months or more before enrollment in the study. Exclusion criteria were (1) pregnancy or having plans to become pregnant, (2) medical problems that could have interfered with outcome variables including cardiovascular and/or metabolic diseases, (3) taking oral contraceptives or hormone therapy, (4) high risk for hysterectomy, and (5) history of drug and/or alcohol abuse. This study received approval from the University of Ottawa and the Montfort Hospital ethics committees, and written consent was obtained from each participant.

### Design

This 5-year Montreal-Ottawa New Emerging Team study was observational and consisted of several visits to the laboratory (year 1: two screening visits [3-4 h each visit], and 3 half-days [3-6 h each visit]). Participants were invited to the laboratory for the following tests and measures: anthropometric and body composition (dual-energy x-ray absorptiometry [DXA]) measurements; stress test for cardiorespiratory fitness; CT scan for body fat distribution; and fasting blood samples for measurement of fasting lipid, insulin, and glucose levels. These measurements were performed annually with the exception of (1) peak oxygen consumption ( $\dot{V}O_{2max}$ ), which was measured in years 1, 3, and 5 and (2) CT, which was not measured in all participants in year 4 and was not performed in year 5. The latter change regarding the study design is caused by the theoretical concern of cancer risk associated with the amount of radiation received from the CT scan, which was considered unethical in a research setting for healthy nonobese women.<sup>17</sup> As a means of standardization, all measurements were performed in the early follicular phase (within 8 days) as long as women still had a regular cycle. Participants were contacted periodically by telephone and postcards throughout the year to establish significant changes concerning their menstrual cycle.

### Status

Menopause status was determined yearly by self-reported questionnaire about menstrual bleeding and its regularity. Follicle-stimulating hormone (FSH) levels were measured annually during the early follicular phase to verify menopause status. Women were classified as premenopausal if they reported no change in menstrual cycle frequency and perimenopausal if they reported changes in menstrual frequency and/or amenorrhea for 3 to 11 months. Finally, women were classified as postmenopausal based on their final menstrual period (FMP) and confirmed by 12 months of amenorrhea.<sup>18</sup>

### Anthropometric assessment

Body weight and height were measured using a BWB-800AS digital scale and a Tanita HR-100 height rod, respectively (Tanita Corporation of America Inc., Arlington Heights, IL). Afterward, BMI was calculated (body weight in

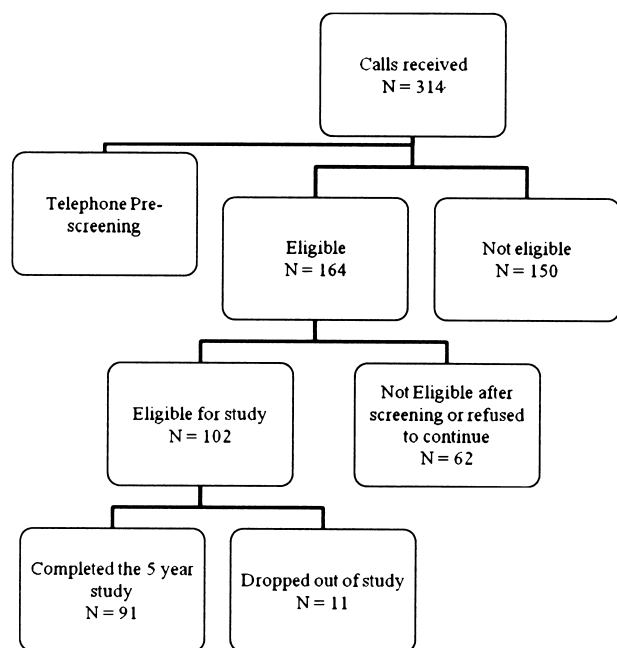


FIG. 1. Recruitment process and sample size of premenopausal women at baseline.

kilograms/height in square meters). Waist circumference (mean of two measures) was determined using a Gulick tape at the middle distance between the lowest rib and the iliac crest measured by four experienced research assistants who were either certified exercise physiologists or registered nurses and followed the guidelines according to the Canadian Society for Exercise Physiology.<sup>19</sup>

FM, percentage FM, trunk FM, and fat-free mass (FFM) were measured using DXA (GE-LUNAR Prodigy module; GE Medical Systems, Madison, WI) as previously described.<sup>20</sup> The coefficient of variation and the correlation for percentage FM measured in 12 healthy participants tested in our laboratory were 1.8% and  $r = 0.99$ , respectively.

VF and AScF were measured using CT (GE High Speed Advantage CT Scanner; General Electric Medical Systems, Milwaukee, WI). Participants had to lie down on an examination table while measurements of the abdomen at the L4 through L5 vertebrate level were performed. VF was quantified by delineating the intra-abdominal cavity at the internal-most aspect of the abdominal and oblique muscle walls. The AScF area was determined by highlighting the adipose tissue located between the skin and the external-most aspect of the abdominal muscle wall.<sup>21</sup> Interobserver coefficient of variation for CT scan is 2.8%. The participants wore a light hospital gown without shoes during the procedure.

### Cardiorespiratory fitness ( $\dot{V}O_2\text{max}$ )

A progressive exercise stress test was performed to measure the participants'  $\dot{V}O_2\text{max}$  on a treadmill. The participants were asked to refrain from any vigorous exercise for 24 hours and consumption of alcoholic beverages for 6 hours before the test. They were also asked to abstain from eating and drinking coffee for 2 hours before the test. The progressive test consisted of 3-minute stages on a treadmill with an increasing workload to the point of exhaustion. After a brief warm-up, participants performed the test protocol. The test was terminated when at least two of the following criteria were achieved<sup>22</sup>: (1) predicted maximal heart rate was reached, (2) respiratory quotient was greater than 1.1, (3) oxygen consumption remained stable or decreased with an increase in workload, or (4) rate of Borg-type scale reached 19 or higher. Peak oxygen consumption was considered as the highest  $\dot{V}O_2\text{max}$  reached during the test.

Heart rate, blood pressure, and the Borg scale<sup>23</sup> were taken at rest and at the end of each stage during the test. Breath-by-breath samples of expired air were collected through a mouthpiece throughout the test, and measurements of oxygen consumption, carbon dioxide consumption, and respiratory exchange ratio were made automatically using a Vmax 229 series metabolic cart (SensorMedics Corporation, Yorba Linda, CA). The indirect calorimetry unit was calibrated according to the manufacturer's specifications before every test to further ensure the reliability of the data collected.

### Resting blood pressure

Supine resting blood pressure was measured manually in the left arm after the participants rested quietly for 5 minutes

using a standard stethoscope and a mercury sphygmomanometer. An appropriate cuff size was selected for each participant based on arm circumference. Assessment of resting blood pressure was standardized according to the American College of Sport Medicine.<sup>22</sup>

### Physical activity energy expenditure

An accelerometer (Actical; Mini Mitter Co., Inc., Bend, OR) was used to estimate mean physical activity energy expenditure (PAEE). During 7 days, the participants wore the accelerometer upon waking up and took it off just before going to bed. Such duration was chosen because it is estimated to result in 90% reliability for the measurement of physical activity in both men and women.<sup>24</sup> The accelerometer was worn on the right hip (anterior to the iliac crest), secured with an elastic belt with the arrow pointing up. That placement, when evaluated along with lower leg or foot, upper leg, head and trunk, lower arm or hand, and upper arm placements, was the best predictor of energy expenditure ( $r = 0.92-0.97$ ).<sup>25</sup> The accelerometers used in this study were validated previously with the use of doubly labeled water measurements.<sup>26</sup> However, even if this tool has been shown to be a good predictor of energy expenditure, we elected to use the time spent in physical activity of varying intensities because, in comparison with energy expenditure, it does not vary across body mass.

### Blood sampling

Fasting samples were taken after a 12-hour overnight fast. Plasma insulin concentrations were determined by radioimmunoassay using <sup>125</sup>I-labeled human insulin and a human insulin antiserum (Millipore, St. Charles, MO). Plasma glucose levels were determined using spectrophotometric analysis after conversion of glucose to glucose-6-phosphate by hexokinase (Sigma-Aldrich Canada Ltd., Oakville, Ontario, Canada; Fisher Scientific Limited, Nepean, Ontario, Canada). IR was estimated using homeostasis model assessment (HOMA) using the following equation:  $\text{HOMA-IR} = (\text{fasting glucose} \times \text{fasting insulin})/22.5$ .

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were analyzed using the Vitros 950 immunoassay analyzer (Ortho Clinical Diagnostics; Johnson & Johnson Company, Markham, Ontario, Canada) at a wavelength of 540 nm. TC, HDL-C, and TG were used in the Friedewald formula to calculate low-density lipoprotein cholesterol (LDL-C) concentrations.<sup>27</sup> Finally, FSH was measured on an automated immunoassay analyzer, the Beckman Coulter Dxl Unicell 800 (Beckman Coulter, Brea, CA). All measures of blood profile presented a coefficient of variation of less than 15%.

### Statistical analysis

SPSS 17.0 for windows (SPSS Inc., Chicago, IL) was used to perform statistical analyses. Variables were first checked for normality, and only TG was log-transformed. Repeated-measures analyses of variance (ANOVA) were used for the determination of the main effects on various variables of interest, having time (years 1, 2, 3, 4, and 5) as a within-subject

factor and menopause status (premenopause, perimenopause, and postmenopause) as a between-subjects factor, adjusted for PAEE. A post hoc test with Games-Howel adjustment was done if there was an effect of status. An ANOVA was used to compare cardiometabolic risk profile between participants with and without increase in VF. Analyses of covariance, adjusted for age, were performed to compare variables of interest between menopause status (premenopause, perimenopause, and postmenopause). A post hoc test with Bonferroni adjustment was used for multiple comparisons. Finally, one-way ANOVAs with post hoc analysis using Bonferroni adjustment were conducted to compare between years before and after FMP in women who became postmenopausal by year 5. Year 0 is considered the year within FMP (menopause onset). Results are expressed as the mean  $\pm$  SD.  $P \leq 0.05$  was considered significant.

## RESULTS

Women's characteristics based on time and menopause status are presented in Table 1. By the end of year 5, 4% ( $n = 4$ ) were still premenopausal (FSH,  $26.5 \pm 24.7$  IU/L), 29% ( $n = 26$ ) were perimenopausal (FSH,  $42.8 \pm 34.5$  IU/L), and 67% ( $n = 61$ ) had become postmenopausal (FSH,  $83.3 \pm 28.8$  IU/L).

According to the repeated-measures analysis of variance (Table 1), a significant main effect of time was observed for total FM, percentage FM, trunk FM, and VF ( $0.05 > P < 0.01$ ), showing an overall increase in time. Furthermore, women who were perimenopausal or postmenopausal by year 3 showed a significant increase in VF ( $P < 0.01$ ) compared with their baseline value (Fig. 2).

A significant effect of time was also observed for plasma HDL-C ( $P < 0.05$ ) and glucose levels ( $P < 0.01$ ); where HDL-C increased and glucose decreased in time (Table 2). Finally, no significant effect of time, status or time  $\times$  status interaction was observed for other variables of interest. After adjustment for PAEE, percentage FM, VF, and total abdominal fat remained significant, with the addition of FFM and WC.

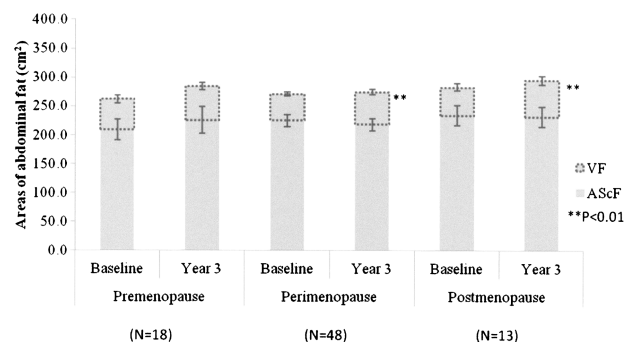


FIG. 2. Abdominal adipose tissue accumulations by time point and menopause status at year 3. The columns represent the total abdominal fat. VF is delimited by a dashed box, and AScF is represented by the value below the dashed box. Values are mean  $\pm$  SD. \*\*Significant difference for VF. VF, visceral fat; AScF, abdominal subcutaneous fat.

However, FM, trunk FM, HDL-C, and fasting glucose no longer presented a significant effect of time (data not shown).

To further analyze the effect of the menopausal transition on body composition and cardiometabolic risk factors, the database was transformed into cases. For premenopause status, only year 1 values were selected; for perimenopause status, values were selected from the last year in which the participant was in that status; and for postmenopause status, fifth-year values were selected, and we performed an analysis of covariance adjusted for age. As a result, postmenopausal women showed significantly higher plasma TC compared with premenopausal and perimenopausal women ( $P < 0.01$ ). In addition, postmenopausal women presented significantly higher plasma HDL-C than did premenopausal women ( $P < 0.05$ ). Finally, both perimenopausal and postmenopausal women present a significantly lower plasma fasting glucose compared with premenopausal women ( $P < 0.01$ ; Fig. 3). Similar results were observed when we performed the same analyses using only values of women who became postmenopausal by the end of the study (data not shown).

Further analysis revealed that women who increased their VF ( $n = 63$ ;  $14.9 \pm 12.6$  cm<sup>2</sup>) during the first 3-year period did

TABLE 1. Body composition characteristics of the population by time point and menopause status at year 5

	Premenopause		Perimenopause		Postmenopause		Repeated-measures ANOVA <i>P</i>		
	Baseline	Year 5	Baseline	Year 5	Baseline	Year 5	Time (y)	Status	Interaction
n	4	4	26	26	61	61			
Age, y	48.3 $\pm$ 0.5	52.3 $\pm$ 0.5	49.1 $\pm$ 1.5	53.2 $\pm$ 1.4	50.3 $\pm$ 2.0	54.4 $\pm$ 2.0			
BW, kg	56.4 $\pm$ 4.5	55.7 $\pm$ 3.8	62.1 $\pm$ 6.1	61.7 $\pm$ 6.6	60.4 $\pm$ 6.4	61.0 $\pm$ 7.3	NS	NS	NS
BMI, kg/m <sup>2</sup>	21.4 $\pm$ 0.7	21.0 $\pm$ 0.8	23.3 $\pm$ 2.0	23.3 $\pm$ 2.2	23.3 $\pm$ 2.3	23.5 $\pm$ 2.9	NS	NS	NS
% FM	22.9 $\pm$ 5.6	26.4 $\pm$ 5.6	31.4 $\pm$ 6.0	32.6 $\pm$ 7.4	31.3 $\pm$ 6.7	33.7 $\pm$ 7.5	<0.01	NS	NS
FM, kg	12.7 $\pm$ 1.9	14.7 $\pm$ 3.0	19.5 $\pm$ 4.7	20.2 $\pm$ 6.0	19.0 $\pm$ 5.3	20.8 $\pm$ 6.5	<0.01	NS	NS
Trunk FM, kg	5.94 $\pm$ 0.7	6.71 $\pm$ 1.8	9.65 $\pm$ 2.7	9.45 $\pm$ 3.7	9.07 $\pm$ 3.1	9.40 $\pm$ 3.8	<0.05	NS	NS
FFM, kg	40.3 $\pm$ 3.4	38.6 $\pm$ 4.7	39.7 $\pm$ 4.5	38.7 $\pm$ 4.4	38.2 $\pm$ 4.0	37.5 $\pm$ 3.5	NS	NS	NS
WC, cm	74.3 $\pm$ 2.3	75.0 $\pm$ 4.5	78.9 $\pm$ 6.1	76.8 $\pm$ 6.7	77.7 $\pm$ 7.1	78.1 $\pm$ 7.0	NS	NS	NS
n	18	18	48	48	13	13			
VF, cm <sup>2</sup>	53.2 $\pm$ 28.0	58.8 $\pm$ 27.1	45.7 $\pm$ 23.3	56.6 $\pm$ 30.4	49.1 $\pm$ 23.0	63.3 $\pm$ 28.8	<0.01	NS	NS
AScF, cm <sup>2</sup>	208.8 $\pm$ 77.1	225.9 $\pm$ 99.5	225.0 $\pm$ 71.2	218.0 $\pm$ 73.1	233.7 $\pm$ 62.7	231.6 $\pm$ 63.4	NS	NS	NS
Total AF, cm <sup>2</sup>	262.1 $\pm$ 99.7	284.7 $\pm$ 122.4	270.7 $\pm$ 83.9	274.6 $\pm$ 94.8	282.8 $\pm$ 78.9	294.9 $\pm$ 83.6	<0.05	NS	NS

Values are mean  $\pm$  SD.

The areas of abdominal fat are between baseline and year 3.

ANOVA, analysis of variance; AF, abdominal fat; AScF, abdominal subcutaneous fat; BW, body weight; BMI, body mass index; FM, fat mass; FFM, fat-free mass; VF, visceral fat; WC, waist circumference; NS, not significant.

**TABLE 2.** Metabolic and physiologic characteristics of the population by time point and menopause status at year 5

	Premenopause		Perimenopause		Postmenopause		Repeated-measures ANOVA <i>P</i>		
	Baseline	Year 5	Baseline	Year 5	Baseline	Year 5	Time (y)	Status	Interaction
n	2	2	25	25	57	57			
FSH, IU/L	7.5 ± 3.5	26.5 ± 24.7	9.1 ± 8.0	42.8 ± 34.5	13.1 ± 13.0	83.3 ± 28.8	<0.01	<0.001	<0.001
TG, mmol/L	0.78 ± 0.08	0.77 ± 0.25	0.93 ± 0.40	0.96 ± 0.42	0.81 ± 0.24	0.85 ± 0.31	NS	NS	NS
TC, mmol/L	3.95 ± 0.35	3.91 ± 0.32	4.36 ± 0.76	4.67 ± 0.74	4.49 ± 0.69	5.07 ± 0.80	NS	NS	NS
HDL-C, mmol/L	1.35 ± 0.14	1.42 ± 0.16	1.52 ± 0.37	1.66 ± 0.38	1.62 ± 0.36	1.83 ± 0.37	<0.05	NS	NS
LDL-C, mmol/L	2.24 ± 0.52	2.14 ± 0.27	2.42 ± 0.68	2.57 ± 0.60	2.49 ± 0.60	2.83 ± 0.66	NS	NS	NS
TC/HDL-C ratio	2.95 ± 0.57	2.77 ± 0.09	3.00 ± 0.77	2.91 ± 0.65	2.89 ± 0.73	2.87 ± 0.70	NS	NS	NS
Fasting glucose, mmol/L	4.90 ± 0.14	4.90 ± 0.00	4.83 ± 0.36	4.60 ± 0.30	4.79 ± 0.39	4.57 ± 0.44	<0.01	NS	NS
Fasting insulin, μU/mL	8.68 ± 3.07	8.45 ± 4.24	12.5 ± 3.02	10.7 ± 2.10	11.8 ± 6.22	11.3 ± 4.05	NS	NS	NS
HOMA-IR	1.90 ± 0.72	1.84 ± 0.92	2.70 ± 0.71	2.18 ± 0.44	2.57 ± 1.47	2.37 ± 0.92	NS	NS	NS
n	4	4	20	20	50	50			
VO <sub>2</sub> max, mL/kg per min	36.9 ± 4.7	33.3 ± 5.6	33.7 ± 7.0	33.1 ± 6.5	33.9 ± 6.2	32.8 ± 6.5	NS	NS	NS
Resting blood pressure									
Systolic, mm Hg	114.0 ± 2.8	117.0 ± 9.9	120.2 ± 11.4	121.1 ± 10.5	115.7 ± 12.3	119.3 ± 12.1	NS	NS	NS
Diastolic, mm Hg	74.0 ± 5.7	72.0 ± 2.8	76.3 ± 7.5	76.6 ± 7.4	72.8 ± 7.5	73.8 ± 7.2	NS	NS	NS

Values are mean ± SD.

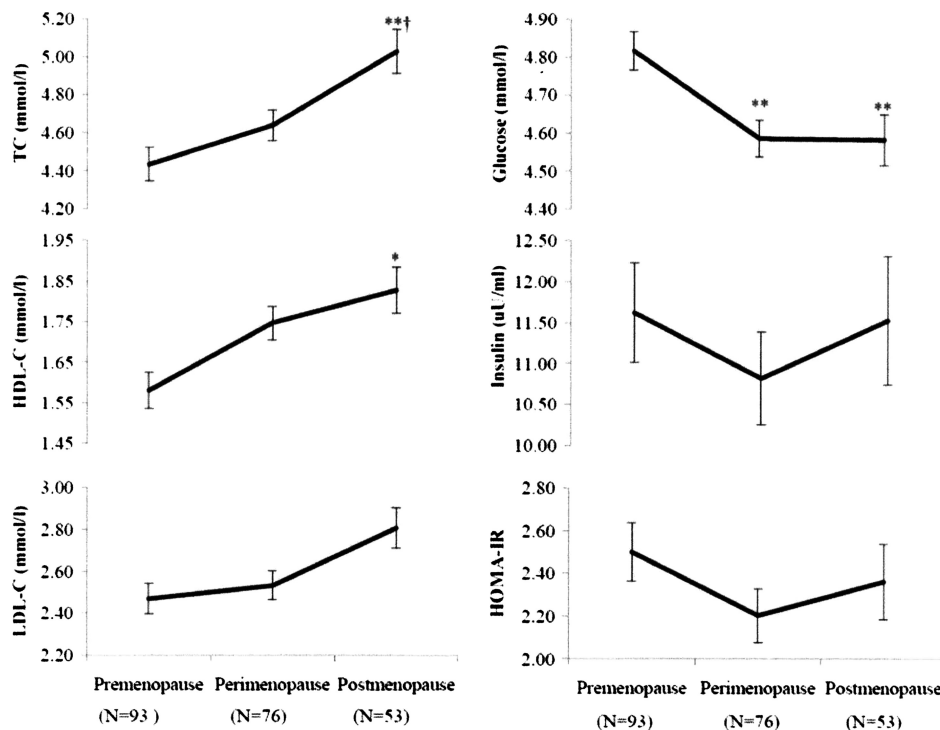
TG values were log-converted for statistical analysis and reconverted for presentation in table format.

ANOVA, analysis of variance; VO<sub>2</sub>max, peak oxygen consumption; HOMA-IR, homeostasis model assessment of insulin resistance; FSH, follicle-stimulating hormone; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant.

not show a significant increase in their cardiometabolic risk profile compared with women who maintained or decreased their VF ( $n = 16$ ;  $-8.6 \pm 8.6 \text{ cm}^2$ ) according to the ANOVA. In addition, no significant correlations were observed between changes in VF and changes in cardiometabolic risk factors (data not shown).

One-way ANOVAs were performed to investigate the differences between years relative to FMP in women who have

become postmenopausal by the end of the study. Year 0 is the year within the FMP, or menopause onset; year 1 is considered as 1 year after FMP, year -1 is considered as 1 year before FMP, and so on. As a result, we did not observe any significant difference between year 0 (menopause onset) and any other year for measures of body composition (Table 3). However, TC was significantly lower at years -3 and -2 ( $P < 0.01$ ). HDL-C and LDL-C were significantly lower, and



**FIG. 3.** The effect of menopause status on metabolic profile in women. For premenopause status, only year 1 values were selected; for perimenopause status, values were selected from the last year in which the participant was in that status; and for postmenopause status, the fifth-year values were selected. Data are adjusted for age. \*Significantly different from premenopause ( $P < 0.05$ ); \*\*Significantly different from premenopause ( $P < 0.01$ ); †Significantly different from perimenopause ( $P < 0.05$ ). TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR; homeostasis model assessment of insulin resistance.

TABLE 3. Body composition changes since final menstrual period

	Years since final menstrual period						
	-4	-3	-2	-1	0	1	2
n	20	44	60	59	59	38	16
BW, kg	58.6 ± 6.7	59.8 ± 7.0	60.4 ± 6.7	60.6 ± 7.2	60.6 ± 7.0	61.8 ± 7.2	61.5 ± 6.4
BMI, kg/m <sup>2</sup>	23.0 ± 2.3	23.0 ± 2.5	23.3 ± 2.3	23.4 ± 2.6	23.4 ± 2.7	23.6 ± 2.9	23.6 ± 2.9
% FM	27.9 ± 6.9	30.3 ± 6.9	31.4 ± 6.6	31.9 ± 7.5	32.7 ± 7.3	35.2 ± 7.4	35.6 ± 6.2
FM, kg	16.5 ± 5.6	18.3 ± 5.6	19.1 ± 5.4	19.5 ± 6.1	19.9 ± 6.1	21.9 ± 6.3	21.9 ± 5.6
FFM, kg	38.3 ± 4.5	38.7 ± 3.7	38.5 ± 3.8	38.2 ± 3.9	37.8 ± 3.6	37.1 ± 3.7	36.8 ± 2.9
WC, cm	76.3 ± 8.0	76.8 ± 6.6	77.8 ± 7.3	77.7 ± 7.2	78.1 ± 6.8	79.4 ± 7.2	78.4 ± 8.3

Values are mean ± SD.

None of the values were significantly different from 0.

BW, body weight; BMI, body mass index; FM, fat mass; FFM, fat-free mass; WC, waist circumference.

glucose was significantly higher at year -3 compared with year 0 ( $P < 0.05$ ; Table 4).

We did not observe any significant effect of time, menopause status, and overall change for non-HDL-C.

### DISCUSSION

The major finding and perhaps the most novel contribution of the present longitudinal study is that changes in body composition and fat distribution can occur in nonobese premenopausal women as they go through the menopausal transition, but these are not necessarily accompanied by cardiometabolic risk factor deteriorations. Such a finding suggested that in healthy nonobese premenopausal women, the menopausal transition would not necessarily have a negative impact on the cardiometabolic risk factors.

Our results confirmed our primary hypothesis that women going through the menopausal transition would show an increase in VF even after adjustment for PAEE. These results extend the findings from previous studies demonstrating that postmenopausal women display higher body fat and abdominal fat compared with premenopausal women.<sup>3,12,28-31</sup> However, to our knowledge, none of the longitudinal studies to date have investigated the effect of the menopausal transition on nonobese women using gold standard techniques to measure body composition and body fat distribution. In fact, most

of the studies have either been cross-sectional or longitudinal and used weight and/or BMI as a primary endpoint. However, one study conducted by Lovejoy et al.<sup>12</sup> reported similar results to ours in 129 premenopausal women. They observed significant increases in total abdominal fat and VF after a 4-year follow-up. Moreover, 40% of their women became postmenopausal by the end of the study. However, compared with the latter study cited above, our participants were thinner (BMI,  $23.3 \pm 2.2$  kg/m<sup>2</sup> vs  $27.1 \pm 0.6$  kg/m<sup>2</sup>).

The body composition and fat distribution changes observed during the menopausal transition can be explained, in part, by the decline of estrogen levels that is associated with menopause.<sup>12</sup> The direct effect of estrogen is through the inhibition of adipose depot by decreasing lipogenesis and lipoprotein lipase activity.<sup>32</sup> It could also relate to physiologic and/or behavioral changes in a woman's life because of changing ovarian hormone status.<sup>33</sup> For example, factors such as decreased resting metabolic rate and/or alterations in energy intake and appetite may play causative roles in total and central fat gain during menopause.<sup>33,34</sup> Age can be another factor that explains the changes in body composition and fat distribution in women. Studies have reported that weight gain and increase in BMI and WC are caused by the effect of aging and not by the menopausal transition.<sup>35-37</sup> We did not observe such results for weight, BMI, and WC in our group of women, probably

TABLE 4. Fasting metabolic profile changes since the final menstrual period

	Years since final menstrual period						
	-4	-3	-2	-1	0	1	2
n	20	43	59	58	57	38	15
FSH, IU/L	12.9 ± 14.4 <sup>a</sup>	13.6 ± 8.2 <sup>a</sup>	24.9 ± 20.9 <sup>a</sup>	48.7 ± 32.6 <sup>a</sup>	85.2 ± 31.7	89.1 ± 27.4	90.3 ± 33.3
TG, mmol/L	0.77 ± 0.25	0.79 ± 0.26	0.78 ± 0.27	0.80 ± 0.45	0.82 ± 0.38	0.85 ± 0.48	0.93 ± 0.37
TC, mmol/L	4.45 ± 0.54	4.34 ± 0.63 <sup>a</sup>	4.52 ± 0.66 <sup>a</sup>	4.74 ± 0.66	5.04 ± 0.82	5.04 ± 0.80	5.20 ± 1.04
HDL-C, mmol/L	1.66 ± 0.33	1.58 ± 0.34 <sup>b</sup>	1.67 ± 0.34	1.76 ± 0.33	1.82 ± 0.34	1.76 ± 0.36	1.77 ± 0.39
LDL-C, mmol/L	2.44 ± 0.46	2.39 ± 0.61 <sup>b</sup>	2.48 ± 0.54	2.62 ± 0.57	2.85 ± 0.72	2.90 ± 0.64	2.92 ± 0.77
TC/HDL-C ratio	2.76 ± 0.51	2.87 ± 0.73	2.80 ± 0.64	2.79 ± 0.68	2.86 ± 0.71	2.97 ± 0.79	3.03 ± 0.85
Fasting glucose, mmol/L	4.80 ± 0.31	4.79 ± 0.37 <sup>b</sup>	4.66 ± 0.43	4.62 ± 0.48	4.51 ± 0.36	4.52 ± 0.53	4.55 ± 0.52
Fasting insulin, μU/mL	9.69 ± 2.50	11.7 ± 7.07	11.0 ± 4.31	11.0 ± 5.41	11.1 ± 3.97	11.8 ± 4.63	11.1 ± 2.89
HOMA-IR	2.06 ± 0.56	2.50 ± 1.66	2.30 ± 0.98	2.28 ± 1.12	2.29 ± 0.84	2.40 ± 1.09	2.27 ± 0.72

Values are mean ± SD.

TG was log-converted for statistical analysis and reconverted for presentation in table format.

FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol.

<sup>a</sup>Significantly different from 0 ( $P < 0.01$ ).

<sup>b</sup>Significantly different from 0 ( $P < 0.05$ ).

because of the differences in population studied. Our group of women was relatively homogeneous, whereas the women in the other studies had a wide range of BMI and multiple ethnic groups as well as a larger sample of participants.<sup>35-37</sup> However, we did observe a significant effect of time for certain variables such as FM, total trunk FM, and VF and after adjustment for PAEE for FFM and WC, which is concordant with results from Lovejoy et al.<sup>12</sup>

Our second hypothesis, however, was not confirmed by our results. We observed no significant difference in the changes in the cardiometabolic risk factors between women with and without increases in VF independent of menopause status as well as no significant associations between changes in VF and changes in cardiometabolic risk factors. On the other hand, even if perimenopausal and postmenopausal women showed increases in VF, they did not show clinical deterioration of their cardiometabolic risk factors. In fact, some metabolic modifications could be considered as protective, such as the increase in HDL-C with time. This finding was unexpected; however, it is consistent with other studies showing a gradual increase in HDL-C up until menopause and then a progressive decline in time.<sup>12,13,38</sup> In fact, our results seem to show that HDL-C somewhat peaked at menopause onset (year 0) and then decreased by 3% in the two following years, even if these changes were not significant. In addition, such an increase in HDL-C can probably be explained by the increase in TC as well as the changes in its subclass profile seen with the menopausal transition as previously described.<sup>39</sup> Furthermore, a decrease in glucose was observed, which is the opposite of what was shown in an animal model study.<sup>40</sup> However, it is consistent with the results reported in one Study of Women's Health Across the Nation study that showed a significant decrease in glucose with time throughout the 9-year study of 949 participants.<sup>11</sup>

A possible reason that may explain why women did not show metabolic deteriorations despite showing changes in metabolic profile is probably related to the observation that the mean VF value was still lower ( $72.4 \pm 40.9 \text{ cm}^2$ ) than the reported thresholds of  $110 \text{ cm}^2$ ,<sup>2,41,42</sup> which is associated with an increased risk of cardiometabolic disturbance in women. In addition, our women were leaner compared with previous studies,<sup>3,10-12</sup> based on BMI. It has been reported that BMI and weight gain that occurs during the menopausal transition are more closely related to changes in glucose homeostasis<sup>7,9</sup>; in fact, in our cohort, the women who gained weight did show higher change in glucose, but it was not significant (results not shown). However, the mean weight gain in our sample is  $0.28 \pm 3.4 \text{ kg}$ , with individual variation, where 68% are weight stable on a clinical point of view.<sup>43</sup> Furthermore, 67% of women were classified as moderate to highly fit for their age group based on their cardiorespiratory fitness, even after going through the transition, based on the results of the Aerobics Center Longitudinal Study<sup>44</sup> (Table 2). A high level of cardiorespiratory fitness is known to be associated with lower VF and lower rates of metabolic health disturbances, reducing the risk of CVD altogether.<sup>45-47</sup>

The present study failed to show a significant effect of the menopausal transition on resting blood pressure; such an outcome can be explained by the fact that our population was relatively lean at baseline and after follow-up.<sup>48</sup> Finally, knowing that the duration of the postmenopausal period is one of the determinants of cardiometabolic profile, a longer follow-up may have been helpful to observe metabolic deteriorations in our sample of healthy nonobese women.<sup>49</sup>

Our study presents certain limitations. First, the population consisted of healthy women with a BMI less than  $30 \text{ kg/m}^2$ . Therefore, our findings cannot be generalized to the whole population. However, it is important to mention that 45% of the women aged between 40 and 59 years in the Canadian population present a BMI between 20 and  $29 \text{ kg/m}^2$ . Second, the amounts of VF and AScF were not measured at year 5 and were only measured in a small subgroup of participants at year 4; thus, the interpretation should be taken cautiously. Finally, the number of women in the premenopausal group decreased throughout the study, slightly reducing power; however, this is expected because the women selected would most probably become postmenopausal by the end of this prospective study. Nevertheless, the present study is strengthened by the well-characterized cohort of women. Throughout the 5 years, there was only a 10% dropout. We also used gold-standard measuring methods (DXA and CT scan) for the measurement of body composition and abdominal fat. Throughout the study, 96% of the women are either in transition or have become postmenopausal.

## CONCLUSIONS

In conclusion, our results suggest that changes in body composition and fat distribution can occur in nonobese women as they go through the menopausal transition. However, these changes were not accompanied by cardiometabolic deteriorations.

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## CHAPTER 5

### **ARE VASOMOTOR SYMPTOMS ASSOCIATED WITH GREATER ALTERATIONS IN CARDIOMETABOLIC RISK FACTORS AND INFLUENCED BY PHYSICAL ACTIVITY IN WOMEN TRANSITIONING TO MENOPAUSE? A MONET GROUP STUDY**

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(Manuscript in preparation)

Author contributions:

Martin Brochu, Éric Doucet and Denis Prud'homme participated in the development of the research project (MONET). Joseph Abdunour participated in the data collection. Joseph Abdunour and Denis Prud'homme performed the analysis and interpretation and completed the writing of the manuscript. All authors were involved in the revision and interpretation of the paper.

**Are Vasomotor Symptoms Associated with Greater Alterations in Cardiometabolic Risk Factors and Influenced by Physical Activity in Women Transitioning to Menopause? A MONET Group Study**

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## ABSTRACT

**Introduction:** Conflicting results have been reported concerning the prevalence of cardiometabolic risk factors in women experiencing vasomotor symptoms (VMS) as well as the influence of physical activity levels during the transition to menopause. **Objectives:** 1) To compare body composition, body fat distribution and cardiometabolic risk factors between women with and without VMS during the menopause transition and 2) To determine the influence of physical activity levels on the prevalence of VSM. **Methods:** Secondary data analyses of a prospective 5-year cohort study. Yearly assessment of women transitioning through menopause included self-reported VMS (hot flashes and night sweats), body composition, body fat distribution, fasting plasma glucose and insulin, lipids, and physical activity levels. **Results:** 85 of the 102 premenopausal women at baseline were included and had a mean age of  $49.9 \pm 2.0$  years with a BMI of  $23.2 \pm 2.2$  kg/m<sup>2</sup> and % body fat of  $31.4 \pm 6.3$  %. Only data of the first four years were used because of the low response rate (5%) for the post-cards documenting VSM in the last year of the study. According to repeated measures ANOVA, no statistically significant differences were observed for weight, fat mass, lean body mass, body fat distribution and cardiometabolic risk factors, when comparing symptomatic vs. asymptomatic women. However, symptomatic women had significantly lower % body fat compared to those without VMS. Neither physical activity levels nor intensity were associated with the prevalence of VMS. **Conclusion:** Our results suggest that women transitioning through menopause who reported VMS did not show greater deteriorations in body composition, body fat distribution and cardiometabolic risk factors. Furthermore, physical activity levels were not associated with lower prevalence of vasomotor symptoms in the present cohort.

## INTRODUCTION

Menopausal vasomotor symptoms (VMS) are defined as episodes of intense heat perception followed by sweating and flushing (e.g., hot flashes and night sweats)<sup>1</sup>. Such condition results from the inability to regulate an optimal body temperature and is known to affect women who go through the menopause transition<sup>2,3</sup>. It has been reported that around the onset of menopause, 85% of women complained of VMS, which then declines slowly to reach 57% after 10 years in postmenopause<sup>4</sup>.

Several studies have shown an association between VMS and cardiovascular disease (CVD)<sup>5-8</sup>, which is known to be the leading cause of mortality among women of this age group in developed countries<sup>6</sup>. While some studies showed independent association between CVD and hot flashes<sup>1,9</sup>, and others with night sweats<sup>6,10</sup>, the majority of the evidence showed that women experiencing both conditions present higher prevalence of obesity, abdominal obesity, hypertension, dyslipidemia, hyperglycemia, hyperinsulinemia, and type 2 diabetes<sup>3,5,11-14</sup>. The reasons for the difference observed concerning the link between hot flash and/or night sweat and CVD is not clear. On the other hand, one study showed no association between cardiometabolic risk factors and the incidence of VMS in women<sup>15</sup>. These differences could be due to the characteristics of the population studied. The majority of studies included women with a wide range of BMI and % body fat<sup>1,5,10,13,16</sup> from multi ethnic population<sup>1,8,11,13,16</sup>, and have mostly used a cross-sectional study design<sup>4, 8-10, 12, 15</sup>. Furthermore, a small number of studies used bioelectric impedance to estimate body composition (e.g. to measured fat mass and lean mass)<sup>1,12,16</sup>, while the majority did not report valid measures of body composition and/or body fat distribution<sup>5,8,10,11,13,15,17</sup>.

Although physical activity is believed to improve VMS by altering the thermoregulatory function during menopause transition<sup>18</sup>, studies have also shown contradicting results. While some studies showed negative relationships between physical activity levels and VMS<sup>19-22</sup>, others reported no association<sup>23-27</sup>. Possible reasons for such equivocal results may be due to the difference in assessment and/or mode of physical activity levels between studies. This makes it difficult to ascertain definitive conclusions on the effects of physical activity levels or intensity on the incidence and prevalence of VMS in women transitioning to menopause<sup>28</sup>. The objectives of this study were 1) to compare body composition, body fat distribution, and cardiometabolic risk factors in non-obese premenopausal women with and without VMS, and 2) to determine the influence of physical activity levels and intensity on the prevalence of VMS throughout the menopause transition. Our hypothesis was that women experiencing VMS during menopausal transition, specifically hot flashes and/or night sweats, would show higher levels of adiposity and cardiometabolic risk factors. Also, high physical activity levels would be associated with a lower prevalence of vasomotor symptoms.

## **METHODS**

### **Study design**

The study is a secondary data analysis of a 5 year longitudinal MONET (Montreal Ottawa New Emerging Team) study<sup>29</sup>. Briefly, this study recruited healthy premenopausal women aged between 47 and 55 years. The participants' inclusion/exclusion criteria have been previously published<sup>29</sup>. Among the original 102 participants, 11 dropped out and 6 did not have a complete data set; which left us with 85 participants for the present study. However, baseline characteristics were not different compared to the original study participants (data not shown). This study was conducted according to the guidelines of the Declaration of Helsinki, and received the approval from the University of Ottawa and the Montfort Hospital Ethics committees.

### **Outcome measures:**

#### **Status**

Menopausal status was determined yearly by self-reported questionnaire about menstrual bleeding and regularity. Women were classified as premenopausal if they reported no change in menstrual cycle frequency and perimenopausal if they reported changes in menstrual frequency and/or amenorrhea for 3-11 months. Finally, women were classified as postmenopausal based on 12 consecutive months of amenorrhea and a FSH levels > 30 IU/liter<sup>30</sup>.

### **Subjects' categorization**

Participants were first classified into two groups according to VMS status: 1) asymptomatic, women who did not report experiencing VMS throughout the 4 year observation period of the study and 2) symptomatic, women who reported having experienced VMS (hot flashes and/or night sweats). Participants were then re-classified into four sub-groups, participants who: 1) were asymptomatic, 2) had hot flashes only, 3) had night sweats only and 4) had hot flashes and night sweats.

### **Vasomotor Symptoms**

Hot flashes and night sweats were assessed continuously throughout the study via self-reported questionnaire using 4 post-cards (one post-card per 3 months): “Have you experienced any hot flashes and/or night sweats?” and “If you did experience hot flashes and/or night sweats, how many days did you have them?” Response options were “no” or “yes”; number of days. We dichotomized the responses in two categories (asymptomatic vs. symptomatic) for hot flashes and/or night sweats. Then, we classified women as “asymptomatic” or “symptomatic” if they answered “no” or “yes” in the post-cards throughout the follow-up study, respectively. Because of the low response rate (5%) for the post-cards in the last year of the study compared to the response rate in the first 4 years (50% to 92%), only the data of the first four years were used for the present study.

### **Anthropometric assessment**

Body weight and height were measured every year with a BWB-800AS digital scale and a Tanita HR-100 height rod (Tanita Corporation of America, Inc., Arlington Heights, IL),

respectively. Body mass index (BMI) was then calculated [body weight (kg)/height (m<sup>2</sup>)]. Waist circumference (mean of two measures) was determined using a Gulick tape at the mid-distance between the lowest rib and the iliac crest<sup>31</sup>. Fat mass, % body fat, lean body mass and trunk fat mass were measured using dual-energy x-ray absorptiometry (DEXA) (GE-LUNAR Prodigy module, GE Medical Systems, Madison, Wi, USA).

### **Physical activity levels**

An accelerometer (Actical; Mini Mitter Co, Inc, Bend, OR) was used to measure mean physical activity levels in kcal/day and time spent in physical activity of various intensities (sedentary, light, moderate and vigorous) per week. Sedentary was described as an intensity between 1.0 and 1.5 METs, light intensity > 1.5 METs and < 3.0 METs, moderate intensity  $\geq$  3.0 METs and < 6.0 METs, and vigorous intensity  $\geq$  6.0 METs<sup>32</sup>. Once a year, participants wore the accelerometer upon waking up and took it off just before going to bed for 7 consecutive days, as previously described<sup>29</sup>. Daily activity levels measured via accelerometry were found to be a good predictor of energy expenditure ( $r = 0.92 - 0.97$ )<sup>33</sup>. The accelerometers used to measure physical activity energy expenditure in this study were also validated with the use of doubly labeled water measurements<sup>34</sup>.

### **Blood sampling**

Annual blood samples were taken after a 12-h overnight fast. Data regarding plasma insulin and glucose concentrations, as well as lipids (total cholesterol, high-density lipoproteins cholesterol, low-density lipoproteins cholesterol and triglycerides) were previously reported<sup>29</sup>. Insulin resistance was estimated using the homeostasis model assessment

[HOMA-IR = (fasting glucose x fasting insulin)/22.5]<sup>35</sup>. Finally, follicle-stimulating hormone was measured on an automated immunoassay analyzer (Beckman Coulter, Brea, DxI Unicell 800, CA).

### **Statistical analysis**

SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA) was used to perform statistical analyses. Variables were verified for normality. Consequently, only triglycerides values were log-transformed to normalize the distribution. *Repeated measures ANOVA* were performed to determine the main effects on body weight and various indices of body composition, body fat distribution, cardiometabolic risk factors and physical activity. *Time* (baseline vs. year 4) was considered as *within-subject* factor; *VMS* (asymptomatic vs. symptomatic) was considered as *between-subject* factor. *Repeated measures ANOVA* were performed comparing the sub-groups for the various variables of interest. A *post-hoc* test with *Games-Howell* adjustment was used for multiple comparisons if a main effect was observed for *VMS* groups. *Binary logistic regressions* were performed to assess the related risk factors for *VMS* (presence vs. absence). Menopause status at year 4 (premenopause, perimenopause and postmenopause), changes (year 4 - baseline) in % body fat, waist circumference and trunk fat mass, as well as physical activity levels and intensities were considered as factors. Physical activity levels and intensities were averaged and divided into tertiles. Results are expressed as the mean  $\pm$  standard deviation and odds ratio (OR) with 95% confidence intervals (CI). A *P* value  $\leq 0.05$  was considered as significant.

## RESULTS

Baseline characteristics of the 85 premenopausal women are presented in Table 1. 77 (88.5%) women reported VMS during the menopause transition. Among the symptomatic women 5 (6.5%) were still premenopausal, 37 (48.1%) were perimenopausal and 35 (45.5%) were postmenopausal at year 4 follow-up. A sub-group (N = 57) of women specifically reported experiencing hot flashes only (N = 23 (40.4%)); night sweat only (N = 22 (38.6%)); and both (N = 12 (21.1%)).

Apart from observing an effect of time on several indices of body composition and cardiometabolic risk factors, no significant differences were observed for various measures of interest between women with and without VMS (Table 2). However, compared to asymptomatic women, symptomatic ones presented a lower % body fat ( $31.4 \pm 7.8$  % vs.  $37.7 \pm 3.0$ ;  $P < 0.05$ ). When women were re-classified into four sub-groups based on the absence and type of VMS, there were no significant differences on any of the variables of interest (Table 3). Also, no significant *time* x *VMS* interactions was observed.

Further analyses revealed that the menopause status was significantly related to the presence of VSM. Actually, perimenopausal women were 6 times (OR: 5.83, CI 95% [1.08 – 31.38];  $P < 0.05$ ) and postmenopausal women were 15 times (OR: 15.11, CI 95% [2.25 – 101.68];  $P < 0.01$ ) more likely to experience VMS compared to premenopausal women. Changes in % body fat, waist circumference and trunk fat were not significant risk factors related to the presence of VMS (Table 4). The average physical activity levels (tertile) and time spent doing vigorous physical activities (tertile) were not associated with a lower risk of VMS.

Also, no association was observed for the time spent doing light or moderate physical activities (data not shown).

## DISCUSSION

Vasomotor symptoms are considered to be the hallmark of menopause transition in women<sup>6</sup>. However, the causes of VMS remain unclear. It is postulated that women who experience VMS have a narrower thermoregulatory zone<sup>36</sup>, as well as a miscommunication in the signaling between the core body temperature, brain and vascular system<sup>37</sup>. This further leads to an exaggerated activation of heat dissipation responses, which includes vasodilation and sweating<sup>37</sup>. In the present cohort, 88.5% of women reported experiencing VMS (hot flashes and/or night sweats) at one point or more throughout the 4-year follow-up. This proportion of symptomatic women is similar to the percentage reported in the Study of Women's Health Across the Nation (SWAN) study, where 60% to 80% of them experienced VMS during the menopause transition<sup>38</sup>.

Previous studies reported that symptomatic women presented higher BMI, lipids and lipoproteins levels<sup>5, 10, 12, 13</sup>. The adverse cardiometabolic risk profile observed in women reporting VMS is thought to be caused by an increased activity of the sympathetic nervous system<sup>5, 13</sup>, which has been associated with an increased secretion of cortisol, catecholamines (norepinephrine) levels and free fatty acids. The latter have been associated with obesity and cardiometabolic risk factors<sup>39</sup>. Interestingly, results of the present study showed that women who experienced VMS did not have higher levels of adiposity or a worse cardiometabolic profile compared to women without VMS. Such results led us to reject our hypothesis, and go against results previously reported in the literature<sup>5, 10, 12-14</sup>. In a cross-sectional study, Gast *et al.*<sup>5</sup> reported that women aged between 46 and 57 years with VMS, had a higher BMI and total cholesterol levels. In another cross-sectional study by the same group, but in a different cohort; the authors reported that women aged between 50 and 64 years, with VMS

(mostly night sweats), had a higher waist-to-hip ratio, plasma glucose, low-density lipoprotein cholesterol and triglyceride levels compared to women without VMS<sup>10</sup>. Results from the SWAN study<sup>13</sup> indicated that the presence and frequency of VMS after 8 years was associated with higher lipid and lipoprotein levels in women aged between 42 and 52 years at baseline.

However, despite observing a lower % body fat in symptomatic women in our study, the change in % body fat according to the binary regression model was not associated with the prevalence of VMS. Similar results were noted regarding changes in waist circumference and trunk fat mass during the 4-year follow-up. Such results are contrary to what has been reported in some cross-sectional<sup>14, 16, 17, 40</sup> and longitudinal<sup>1</sup> studies where high levels of body fat and abdominal fat have been found to be associated with a greater prevalence of hot flashes and night sweat. Body fat is thought to play an insulator role, where women with high body fat mass or % body fat tend to experience more events of heat dissipation<sup>1</sup>. In the SWAN study, the authors found that % body fat gain (measured by bioelectric impedance) adjusted for confounding variables was associated with greater odds of reporting hot flashes (odds ratio = 1.23, 95% CI: P = 0.03) in 1,659 women after 4 years<sup>1</sup>. In another study conducted in 274 postmenopausal women (age: 54.5 ± 5.3 years), those displaying an android body fat distribution (determined by a high waist-hip ratio) experienced more VMS compared to women with a gynoid phenotype<sup>40</sup>. It was then suggested that high body fat mass, android body fat distribution, testosterone levels and low levels of estradiol in women going through menopause transition increased the prevalence of VMS<sup>40</sup>. High body fat, specifically in the abdominal region, is known to secrete multiple cytokines which have been found to be associated with VMS in women<sup>41</sup>.

Certain reasons may partly explain the conflicting results between the present study and what was previously reported in the literature. First, our sample was composed of healthy non-obese women. Actually, as previously reported by our group in the present cohort, increases in % body fat and visceral fat accumulations after the follow-up period were not associated with metabolic deteriorations<sup>29</sup>. Additionally, our cohort was composed of leaner women compared to other studies<sup>1, 5, 10, 13, 14, 16</sup>, either based on BMI or % body fat. Finally, the majority of our women were classified as physically active based on the accelerometer cut-off and moderate to highly fit for their age group based on their cardiorespiratory fitness<sup>29</sup>. In fact, high cardiorespiratory fitness is known to be associated with lower adiposity and visceral fat accumulations, as well as with a better cardiometabolic profile<sup>42-45</sup>. Among the risk factors that were assessed in this study, menopausal status (perimenopause and postmenopause) was the only one that was associated with increased risk of VMS. This follows the traditional belief of menopause transition and VMS, which is most likely due to the changes in reproductive hormones (progressive reduction in estrogen levels) in women going through the menopause transition<sup>2, 38</sup>. One longitudinal study reported that among the many factors assessed (age, education, BMI, smoking and baseline anxiety), the transition to menopause was strongly associated with VMS in women enrolled in the SWAN study<sup>38</sup>. Furthermore, we showed that physical activity level and time spent in varying intensities were not significantly associated with VMS. While this is in contradiction with results from previous studies<sup>19-22</sup>, the null findings in the present study do agree with other<sup>23-26</sup>. For instance, results from one trial showed that symptomatic women aged between 48 and 57 years (randomized to either exercise intervention programs or control group) showed no significant difference in the reporting of VMS after a 6-month follow-up<sup>23</sup>. Another study

showed that a 12-week moderate-intensity aerobic exercise intervention had no effect on the prevalence of VMS in late perimenopausal and postmenopausal women aged between 40 and 62 years<sup>25</sup>. Finally, a systematic review by Daily *et al.*<sup>46</sup> concluded that there was insufficient evidence to show whether exercise is an effective treatment for VMS.

Our study presents certain limitations worthy of discussion. First, the population studied consisted of healthy women with a BMI < 30 kg/m<sup>2</sup>. Therefore, our findings cannot be generalized to the whole population with a wide range of BMIs. Second, VMS were self-reported by means of a questionnaire, in which women recalled symptoms and reported them using post-cards. Despite such method being widely used in research, these measures are relatively more prone to reporting biases compared to the use of a diary<sup>47</sup> or physiologic measures such as sternal skin conductance system (which objectively measures hot flashes)<sup>48</sup>. Third, our small sample size compared to previous studies<sup>1, 5, 10, 13, 16</sup> might have reduced power to detect significant associations. Nonetheless, our study presents several strengths. The rigorous assessment of qualitative and quantitative physiological endpoints (i.e., well phenotyped group) allowed us to examine a well-characterized cohort of women that was longitudinally followed during the menopause transition. Most of the other studies were cross-sectional<sup>5, 10, 12, 16, 17, 40</sup>, which do not allow for conclusion of a cause-and-effect relationship. Concerning longitudinal studies<sup>1, 11, 13</sup>, they did not use gold standard methods to measure body composition, body fat distribution and/or physical activity levels. Unlike the latter studies, we used DEXA (a valid and reliable method to measure body composition and body fat distribution)<sup>49</sup> and an accelerometer to objectively measure physical activity levels and intensities<sup>34, 50</sup>.

## **CONCLUSION**

Our results suggest that women transitioning through menopause who report VMS do not show greater deteriorations in body composition, body fat distribution and cardiometabolic risk factors after 4 years follow-up. Furthermore, physical activity levels and intensity were not associated with lower prevalence of vasomotor symptoms in the present cohort. Further studies are needed to confirm our results.

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**CONFLICT OF INTEREST**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Baseline anthropometric and cardiometabolic characteristics of pre-menopausal women.

Variables	Mean $\pm$ SD	Minimum	Maximum
N	85		
Age (yrs)	49.9 $\pm$ 2.0	47	55
<b>Body composition</b>			
Body mass index (kg/m <sup>2</sup> )	23.3 $\pm$ 2.2	19.3	28.7
% Body fat	31.4 $\pm$ 6.3	18.2	41.7
Fat mass (kg)	19.1 $\pm$ 5.0	9.6	29.8
Lean body mass (kg)	38.8 $\pm$ 4.0	31.2	50.1
Waist circumference (cm)	78.1 $\pm$ 6.6	62.2	93.7
Trunk fat (kg)	9.2 $\pm$ 2.8	3.3	16.2
<b>Metabolic profile</b>			
Triglycerides (mmol/l)	0.85 $\pm$ 0.29	0.41	1.98
Total cholesterol (mmol/l)	4.44 $\pm$ 0.68	3.05	6.23
HDL-C (mmol/l)	1.57 $\pm$ 0.34	0.81	2.36
LDL-C (mmol/l)	2.47 $\pm$ 0.61	1.33	4.25
TC/HDL-C	2.94 $\pm$ 0.73	1.78	5.40
Fasting Glucose (mmol/l)	4.80 $\pm$ 0.37	3.80	5.70
Fasting Insulin (uU/ml)	11.81 $\pm$ 5.41	5.03	47.37
HOMA-IR	2.54 $\pm$ 1.27	1.14	11.16
<b>Measures of physical activity</b>			
N	75		
Physical activity levels (kcal/day)	807.7 $\pm$ 262.0	326.3	1904.7
Time spent in varying physical activity intensities (min/week)			
Light	1764.3 $\pm$ 318.1	971.0	2680.0
Moderate	1621.8 $\pm$ 483.6	628.0	2801.0
Vigorous	69.6 $\pm$ 106.4	0	607

N: number of participants (number differ because of missing data); HDL-C: high-density lipoproteins cholesterol; LDL-C: low-density lipoproteins cholesterol; TC: total cholesterol; HOMA-IR: homeostasis model assessment; VMS; vasomotor symptoms.

Table 2. Effect of reporting vasomotor symptoms during menopause transition on adiposity indices and cardiometabolic risk factors.

	Baseline		Year 4		2 x 2 Anova		
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Time	VMS	Time x VMS
N	9	76	9	76			
<b>Body composition</b>							
Body weight (kg)	60.9 ± 5.7	60.8 ± 6.3	62.5 ± 4.7	60.8 ± 7.0	NS	NS	NS
Body mass index (kg/m <sup>2</sup> )	23.8 ± 1.9	23.2 ± 2.2	24.4 ± 1.5	23.3 ± 2.6	NS	NS	NS
% Body fat	35.2 ± 4.2	30.9 ± 6.4	37.7 ± 3.0	31.4 ± 7.8	<0.05	<0.05	NS
Fat mass (kg)	21.4 ± 4.1	18.8 ± 5.0	23.4 ± 3.0	19.4 ± 6.2	<0.05	NS	NS
Lean body mass (kg)	36.6 ± 2.6	39.1 ± 4.1	36.2 ± 2.3	38.8 ± 4.2	NS	NS	NS
Waist circumference (cm)	77.6 ± 8.0	78.2 ± 6.5	79.4 ± 7.3	77.5 ± 7.5	NS	NS	NS
Trunk fat (kg)	10.0 ± 2.6	9.1 ± 2.9	9.8 ± 2.7	8.0 ± 3.6	NS	NS	NS
N	9	75	9	75			
<b>Metabolic profile</b>							
Triglycerides (mmol/l)	0.83 ± 0.31	0.85 ± 0.29	0.79 ± 0.38	0.83 ± 0.46	NS	NS	NS
Total cholesterol (mmol/l)	4.48 ± 0.74	4.42 ± 0.68	4.69 ± 0.48	4.85 ± 0.79	<0.01	NS	NS
HDL-C (mmol/l)	1.62 ± 0.37	1.57 ± 0.34	1.75 ± 0.40	1.74 ± 0.35	<0.01	NS	NS
LDL-C (mmol/l)	2.48 ± 0.79	2.46 ± 0.59	2.59 ± 0.39	2.73 ± 0.66	<0.05	NS	NS
TC/HDL-C	2.90 ± 0.84	2.94 ± 0.71	2.79 ± 0.65	2.88 ± 0.71	NS	NS	NS
Fasting glucose (mmol/l)	4.69 ± 0.45	4.82 ± 0.35	4.46 ± 0.34	4.47 ± 0.42	<0.01	NS	NS
Fasting insulin (uU/ml)	11.9 ± 3.22 <sup>a</sup>	11.82 ± 5.76 <sup>b</sup>	9.12 ± 2.55 <sup>a</sup>	10.63 ± 3.72 <sup>b</sup>	NS	NS	NS
HOMA-IR	2.54 ± 0.76 <sup>a</sup>	2.55 ± 1.36 <sup>c</sup>	1.81 ± 0.54 <sup>a</sup>	2.13 ± 0.82 <sup>c</sup>	<0.05	NS	NS

Values are mean ± standard deviation. VMS: vasomotor symptoms; N: number of participants; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment; Triglyceride was log-converted for statistical analysis and reconverted for presentation in Table format. <sup>a</sup>N = 7; <sup>b</sup>N = 71; <sup>c</sup>N = 70.

Repeated measures ANOVA; Independent effect of time (within subject factor); Independent effect of VMS (asymptomatic vs. symptomatic) (between subject factors); Time x VMS interaction.

Table 3. Effect of reporting hot flashes and/or night sweats during menopause transition on adiposity indices and cardiometabolic risk factors.

	Baseline				Year 4				2 x 2 Anova		
	Asymptomatic	Hot flashes	Night sweats	Night sweats & hot flashes	Asymptomatic	Hot flashes	Night sweats	Night sweats & hot flashes	Time	VMS	Time x VMS
N	9	22	22	12	9	22	22	12			
<b>Body composition</b>											
Body weight (kg)	60.9±5.7	60.1±6.4	61.5±6.3	61.8±6.1	62.5±4.7	60.5±7.3	61.1±7.3	62.1±6.4	NS	NS	NS
Body mass index (kg/m <sup>2</sup> )	23.8±1.9	23.4±2.6	22.9±2.1	23.3±1.5	24.4±1.5	23.5±3.1	22.9±2.6	23.4±1.9	NS	NS	NS
% Body fat	35.2±4.2	31.9±6.1	30.2±6.5	30.5±6.9	37.7±3.0	32.7±7.4	30.1±8.0	30.7±8.8	NS	NS	NS
Fat mass (kg)	21.4±4.2	19.2±5.0	18.6±5.1	18.9±5.1	23.4±3.0	19.9±6.2	18.6±6.5	19.2±6.6	NS	NS	NS
Lean body mass (kg)	36.6±2.6	38.0±3.8	40.0±4.8	40.1±4.8	36.2±2.3	37.8±4.0	39.7±4.3	40.2±4.7	NS	NS	NS
Waist circumference (cm)	77.6±8.0	77.7±7.1	78.5±5.3	79.8±5.6	79.4±7.3	77.4±9.1	78.4±5.8	78.3±6.5	NS	NS	NS
Trunk fat (kg)	10.0±2.6	9.2±3.2	9.1±2.7	9.4±2.9	9.8±2.7	8.2±3.9	8.0±3.8	8.0±3.6	<0.01	NS	NS
N	9	23	22	11	9	23	22	11			
<b>Metabolic profile</b>											
Triglycerides (mmol/l)	0.83±0.31	0.87±0.27	0.82±0.33	0.80±0.22	0.79±0.38	0.94±0.48	0.77±0.33	0.71±0.23	NS	NS	NS
Total cholesterol (mmol/l)	4.48±0.73	4.69±0.80	4.41±0.59	4.18±0.52	4.69±0.48	5.24±0.95	4.66±0.68	4.61±0.53	<0.01	NS	NS
HDL-C (mmol/l)	1.62±0.37	1.60±0.35	1.61±0.36	1.48±0.25	1.75±0.40	1.78±0.38	1.71±0.30	1.61±0.30	<0.01	NS	NS
LDL-C (mmol/l)	2.48±0.79	2.67±0.67	2.42±0.57	2.33±0.46	2.59±0.39	2.99±0.73	2.60±0.62	2.68±0.52	<0.01	NS	NS
TC/HDL-C	2.90±0.84	3.06±0.80	2.85±0.70	2.88±0.51	2.79±0.65	3.05±0.87	2.80±0.61	2.93±0.52	NS	NS	NS
Fasting glucose (mmol/l)	4.69±0.45	4.84±0.44	4.81±0.26	4.75±0.20	4.46±0.34	4.60±0.38	4.45±0.29	4.49±0.42	<0.01	NS	NS
Fasting insulin (uU/ml)	11.85±3.22 <sup>a</sup>	11.42±5.56 <sup>b</sup>	10.94±2.89 <sup>b</sup>	11.92±2.88 <sup>c</sup>	9.12±2.55 <sup>a</sup>	10.46±3.41 <sup>b</sup>	9.66±2.88 <sup>b</sup>	10.75±2.80 <sup>c</sup>	<0.05	NS	NS
HOMA-IR	2.54±0.76 <sup>a</sup>	2.47±1.26 <sup>b</sup>	2.35±0.65 <sup>b</sup>	2.49±0.65 <sup>c</sup>	1.96±0.54 <sup>a</sup>	2.14±0.70 <sup>b</sup>	1.91±0.60 <sup>b</sup>	2.19±0.77 <sup>c</sup>	<0.01	NS	NS

Values are mean ± standard deviation. VMS: vasomotor symptoms; N: number of participants; FSH: follicle-stimulating hormone; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment. Triglyceride was log-converted for statistical analysis and reconverted for presentation in Table format. <sup>a</sup>N = 7; <sup>b</sup>N = 21; <sup>c</sup>N = 12. Repeated measures ANOVA; Independent effect of time (within subject factor); Independent effect of VMS groups (between subject factors); Time x VMS interaction.

Table 4. Odds ratio associations between vasomotor symptoms and variables of interest.

	Presence of Vasomotor symptoms		
	Odds Ratio	95% Confidence Interval	P Value
<b>Menopause Status</b>			
Premenopause	Referent		
Perimenopause	5.83	1.08 – 31.38	0.04
Postmenopause	15.11	2.25 – 101.68	0.005
<b>Change in % body fat</b>			
Stable <sup>a</sup>	Referent		
Lose	1.09	0.09 – 12.77	0.95
Gain	0.21	0.03 – 1.13	0.07
<b>Change in waist circumference (cm)</b>			
Stable <sup>b</sup>	Referent		
Lose	0.00	0.00	0.99
Gain	3.82	0.72 – 20.38	0.12
<b>Change in trunk fat (kg)</b>			
Stable <sup>c</sup>	Referent		
Lose	1.68	0.32 – 8.97	0.54
Gain	0.36	0.06 – 2.12	0.26
<b>Average physical activity levels (kcal/day)</b>			
Lowest tertile <sup>d</sup>	Referent		
Middle tertile	0.30	0.03 – 3.15	0.36
Highest tertile	0.00	0.00	0.99
<b>Average time spent doing vigorous physical activity<sup>e</sup> (minutes)</b>			
Lowest tertile	Referent		
Middle tertile	1.89	0.16 – 22.79	0.62
Highest tertile	2.00	0.17 – 24.07	0.59

<sup>a</sup> Within  $\pm 1\%$  of change

<sup>b</sup> Within  $\pm 2.5$  cm of change

<sup>c</sup> Within  $\pm 1$  kg of change

Tertiles are based on the 33<sup>rd</sup> and 66<sup>th</sup> percentile.

<sup>d</sup> Lowest tertile  $\leq 713$  kcal/day; middle tertile 714 – 895 kcal/day; highest tertile  $> 895$  kcal/day

<sup>e</sup> Lowest tertile  $\leq 26$  min vigorous PA; middle tertile 26 – 72 min vigorous PA; highest tertile  $> 72$  min vigorous PA.

## CHAPTER 6

### **EXERCISE BLOOD PRESSURE RESPONSE AND CARDIOMETABOLIC RISK FACTORS IN MIDDLE AGED WOMEN: A MONET GROUP STUDY**

JOSEPH ABDULNOUR, MARIE-NOËLLE LACROIX, PIERRE BOULAY, ÉRIC DOUCET, MARTIN BROCHU, RÉMI RABASA-LHORET, JEAN-MARC LAVOIE, DENIS PRUD'HOMME

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Prud'homme participated in the development of the research project (MONET). Joseph Abdulnour and Marie-Noël Lacroix participated in the data collection. Joseph Abdulnour and Denis Prud'homme performed the analysis and interpretation and completed the writing of the manuscript. All authors were involved in the revision and interpretation of the paper.

**Exercise Blood Pressure Response and Cardiometabolic Risk Factors in Middle Aged Women: A MONET Group Study**

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**ABSTRACT**

Objective: to investigate if an exaggerated peak exercise systolic blood pressure (peak ESBP) is associated with alteration of cardiometabolic risk factors and predict future resting hypertension in middle aged women. Methods: data analysis was performed in 95 healthy normotensive premenopausal women at baseline and 84 after 5-year follow-up (age,  $49.9 \pm 1.9$  years; BMI,  $23.3 \pm 2.2$  kg/m<sup>2</sup>; resting BP,  $117/73 \pm 11.8/7.6$  mmHg). Blood pressure was measured at rest and during a progressive exercise test on treadmill. Women were divided into two groups according to their peak ESBP  $<190$  mmHg *vs.*  $\geq 190$  mmHg. Other outcome measures were: cardiorespiratory fitness (VO<sub>2</sub> peak), body composition, body fat distribution and fasting plasma lipids, glucose and insulin levels. Results: 15% and 27% of women presented an exaggerated peak ESBP response ( $\geq 190$  mmHg) at baseline and year 5 respectively. Linear mixed model repeated measures analysis revealed higher values of fasting glucose, resting systolic and diastolic BP in women with an exaggerated peak ESBP ( $\geq 190$  mmHg) compared to women with a peak ESBP ( $<190$  mmHg). No significant difference was observed between the two groups for VO<sub>2</sub> peak, body composition and body fat distribution indices and other cardiometabolic risk factors. Finally, baseline peak ESBP was not a significant risk factor for future resting hypertension (OR: 2.96, 95%CI [0.48-18.12]; P=0.24). Conclusion: our results, despite being non significant, are of great interest because in healthy and active premenopausal women, exaggerated peak ESBP is not predictive of future hypertension after 5-year follow-up throughout menopause transition.

## INTRODUCTION

Hypertension (HT) is one of the major risk factors for cardiovascular diseases (CVD) <sup>1</sup>. The exact causes of essential HT are not identified, but several factors appear to be highly correlated with this clinical condition, including age, family history of HT, smoking, obesity, diabetes, sedentary lifestyle, high sodium intake, high alcohol consumption and stress <sup>2</sup>. Approximately 19% of Canadians over the age of 20 years have HT and its prevalence is constantly on the rise <sup>3</sup>. According to the 2013 Canadian Community Health Survey, the prevalence of HT during mid-life (45-54 years old) is higher in men (20.5%) than in women (15.2%) <sup>4</sup>. However, it is important to note that the prevalence of the HT is under-estimated because of the absence of symptoms in the majority of individuals <sup>4,5</sup>.

Moreover, an exaggerated peak exercise blood pressure (peak EBP) is defined as an abnormally elevated systolic (S) and/or diastolic (D) BP response during exercise testing in individuals with a normal resting BP <sup>6</sup>. Exaggerate EBP response is diagnosed when peak ESBP is  $\geq 190$  and/or peak EDBP  $\geq 105$  mmHg in women and peak ESBP  $\geq 210$  and/or peak EDBP  $\geq 105$  mmHg in men <sup>7,8</sup>. This phenotype has been suggested to be a risk factor for future development of HT at rest in asymptomatic individuals <sup>9,10</sup>. Some researchers have documented various characteristics that are specific to such a phenotype. Among these, the most common are high values of resting systolic and diastolic BP <sup>6,11</sup>, body mass index (BMI) <sup>12,13</sup>, waist circumference <sup>13</sup>, fasting glucose <sup>11,13</sup> and insulin levels, as well as insulin resistance <sup>11,13</sup> and abnormal lipid profile <sup>14,15</sup>.

Most studies that investigated the exaggerated peak EBP in association with cardiometabolic risk factors were cross-sectional <sup>6,9,11-16</sup> and included either only men <sup>10-12,14</sup> or consisted mostly of men <sup>6,9,13,15</sup>. One study appears to have included middle-aged obese

premenopausal women in their analysis on the clinical implications of exaggerated peak EBP response<sup>16</sup>. None of the studies appear to have included non-obese premenopausal women and followed them through the menopause transition. Therefore the objective of this study was to investigate if an exaggerated peak EBP is associated with alteration of cardiometabolic risk factors and predict future resting HT in premenopausal women. We hypothesized that women with an exaggerated peak EBP response would 1) have higher resting SBP and DBP, adiposity and cardiometabolic risk factors, and 2) predict future resting HT in healthy normotensive middle-age women in transition to menopause.

## **METHODS**

### **Subjects**

The study is a secondary data analysis of 102 healthy normotensive premenopausal women aged between 47 and 55 years who participated in a 5-year longitudinal study on the effect of the menopause transition on body composition and CVD risk factors (MONET project, Montreal Ottawa New Emerging Team) <sup>17</sup>. For the purpose of this study, only data from year 1 and year 5 were included in the analysis. Participants were recruited using: 1) community advertising and 2) referrals from the obstetric and gynaecology clinics.

Premenopausal women were included if they met the following criteria: 1) premenopausal status (two menstruations in the last three months, no increase in cycle irregularity in the 12 months preceding testing, and a plasma follicular-stimulating hormone level <30 IU/liter); 2) no surgically-induced menopause; 3) non-smoking; 4) BMI between 20 and 29 kg/m<sup>2</sup>; and 5) reported weight stability ( $\pm 2$  kg) for  $\geq 6$  months before enrolment in the study. Exclusion criteria were: 1) pregnant women or planned to become pregnant; 2) had medical problems that could have interfered with outcome variables including cardiovascular and/or metabolic disease; 3) were taking oral contraceptives or hormone replacement therapy; 4) had high risk for hysterectomy; and 5) had a history of drug and/or alcohol abuse. This study received approval from the University of Ottawa and the Montfort Hospital Ethics committees, and written consent was obtained from each participant.

### **Cardiorespiratory fitness**

A progressive exercise test on a treadmill was performed to measure participants' peak maximal oxygen uptake (VO<sub>2</sub> peak). Participants were asked to refrain from any vigorous

exercise for 24 hours and consumption of alcoholic beverages for 6 hours before the test. They were also asked to abstain from eating and drinking coffee for 2 hours prior to the test. The progressive test consisted of 3-minute stages starting with a speed of 3.4 mph and a slope of 0% with an increasing workload to the point of participant exhaustion (speed increased to 4.0 mph by stage 6, 5.2 mph by stage 8 and 6.0 mph by stage 10; slope increased by 4% at every stage). Heart rate, BP and the rate of perceived exertion (Borg scale)<sup>18</sup> were taken at rest and at the end of each stage during the test. Breath-by-breath samples of expired air were collected through a mouthpiece throughout the test, and measurements of  $\text{VO}_2$  and  $\text{CO}_2$  were made automatically using a Vmax 229 series metabolic cart (SensorMedics Corporation, Yorba Linda, CA). The indirect calorimetry unit was calibrated according to the manufacturer's specifications.

After a brief warm up on the treadmill, subjects performed the exercise test. The test was terminated when at least 2 of the following criteria were achieved<sup>19</sup>: **1)** predicted maximal heart rate for age reached, **2)** respiratory quotient  $> 1.1$ , **3)** oxygen uptake remained stable or decreased with an increase in workload, or **4)** rate of perceived exertion reached  $\geq 19$  (15 points Borg scale). Peak  $\text{VO}_2$  was considered as the highest 30 seconds average  $\text{VO}_2$  reached during the test.

### **Blood pressure**

Qualified research assistants measured supine resting blood pressure manually from the left arm after participants had been resting quietly for 5 minutes using a standard stethoscope and a mercury sphygmomanometer. For this measurement, an appropriate cuff size was selected for each participant based on arm circumference. Assessment of resting blood

pressure was standardized according to the American College of Sport Medicine<sup>19</sup>. SBP was considered as the first detectable Korotkoff sound (phase 1) and DBP was considered as the last detectable Korotkoff sound (phase 5)<sup>20</sup>. Blood pressure during exercise was measured and recorded manually by a trained exercise physiologist using the same equipment, while the subject was being tested on the treadmill. Blood pressure was measured at every stage during the last minute of exercise until the test was stopped. The highest SBP and DBP achieved during the exercise test were defined as the peak ESBP and peak EDBP respectively. An exaggerated BP response to exercise is defined as a peak ESBP response of  $\geq 190$  mmHg and/or peak EDBP response of  $\geq 105$  mmHg as previously described<sup>7,8</sup>. Because none of the participants presented an exaggerated peak EDBP, we focused only on exaggerated peak ESBP.

### **Anthropometric assessment**

Body weight and height were measured with a BWB-800AS digital scale and a Tanita HR-100 height rod, respectively (Tanita Corporation of America, Inc) and BMI was calculated [body weight kg/height (m<sup>2</sup>)]. Waist circumference (mean of two measures) was determined using a Gulick tape at the mid-distance between the lowest rib and the iliac crest.

Fat mass, percent body fat (% BF), lean body mass and trunk fat mass were measured using dual-energy x-ray absorptiometry (DEXA) (GE-LUNAR Prodigy module, GE Medical Systems, Madison, Wi, USA) as previously described<sup>17</sup>. Subjects wore a light hospital gown without shoes for these measurements.

**Blood sampling**

Samples were taken after a 12-h overnight. Plasma insulin concentrations were determined in duplicate by radioimmunoassay using  $^{125}\text{I}$ -labeled Human Insulin and a Human Insulin antiserum (Millipore, St. Charles, MO, USA). Plasma glucose levels were determined using spectrophotometric analysis after conversion of glucose to glucose-6-phosphate by hexokinase (Sigma-Aldrich Canada Ltd., Oakville, ON, CAN; Fisher Scientific Limited, Nepean, ON, CAN). Fasting insulin resistance was also estimated using the homeostasis model assessment (HOMA-IR) equation:  $\text{HOMA-IR} = (\text{fasting glucose} \times \text{fasting insulin})/22.5$ . Total cholesterol (TC), high-density-lipoproteins cholesterol (HDL-C), and triglycerides (TG) were analyzed using the Vitros 950 immunoassay analyzer (Ortho Clinical Diagnostics, Johnson & Johnson Company, Markham, ON, CAN) at a wavelength of 540 nm. TC, HDL-C, and TG were used in the Friedewald <sup>21</sup> formula to calculate low-density-lipoproteins cholesterol (LDL-C) concentration. Finally, FSH was measured using an automated immunoassay analyzer, the Beckman Coulter DxI Unicell 800 (Beckman Coulter, Brea, CA, USA).

**Statistical analysis**

SPSS 17.0 for windows (SPSS Inc. Chicago, IL, USA) was used to perform the secondary statistical analysis. Variables were verified for normality, consequently, only TG was log-transformed to normalize the distribution. The women were divided into two groups: those with a peak ESBP response (<190 mmHg) and those with an exaggerated peak ESBP response ( $\geq 190$  mmHg). A linear mixed model repeated measures analysis was then performed for determination of main effects on various variables of interest. Time (baseline

and year 5) was considered as a *within-subject* factor; and the peak SBP response to exercise was considered as *between-subject* factor. Two-sided Pearson correlations were done to assess the associations between peak ESBP response and cardiometabolic risk factors of interest at baseline. Further associations were done between the changes (year 5 – year 1) in peak ESBP response and the changes in various variables of interest. Finally, a binary logistic regression was performed, with peak ESBP response as an independent factor, to assess whether or not it predicts future resting hypertension. Results are expressed as the mean  $\pm$  standard deviation (Mean  $\pm$  SD) and odds ratio (OR) with 95% confidence intervals. A P value  $\leq 0.05$  was considered as significant.

## RESULTS

Subjects' characteristics based on time and peak ESBP responses are presented in Table 1. Based on resting and exercise BP availability, data analysis was performed in 95 women at baseline and 84 at year 5, respectively. There were no significant differences in the women characteristics and cardiometabolic risk factors between the original cohort and the subsample. To the exception of age, our cohort displayed a broad range of values for the variables of interest. Women presented a mean peak ESBP and EDBP of  $171 \pm 18.1$  mmHg (range: 134 to 248 mmHg) and  $72.8 \pm 8.7$  mmHg (range: 56 to 98 mmHg), respectively.

Fourteen women presented an exaggerated peak ESBP response ( $\geq 190$  mmHg), which represents 15% of the whole cohort at baseline. Nine out of the 14 women and an additional 13 women presented an exaggerated peak ESBP response at year 5 for a total of 22 women (27%).

Linear mixed model repeated measures were performed (Table 1) to determine the main effect of time and peak ESBP response (normal vs. exaggerated) on cardiometabolic risk factors. As a result, a significant main effect of peak ESBP response was observed for fasting plasma glucose and resting systolic and diastolic BP. These variables were significantly higher in participants with an exaggerated peak ESBP response ( $\geq 190$  mmHg) compared to those with a peak ESBP response ( $< 190$  mmHg). Finally, no significant effect of *time* x *peak* ESBP interaction was observed.

Pearson correlation analyses were performed between peak ESBP and EDBP and cardiometabolic risk factors at baseline (Table 2). A significant positive correlation was observed between peak systolic and diastolic EBP and resting SBP and DBP, and a trend between peak ESBP and  $VO_2$  peak ( $p = 0.052$ ). No significant correlations were observed

between the changes in peak ESBP and changes in resting BP, body composition and body fat distribution indices and cardiometabolic risk factors.

Finally, only 2 (14%) of the women with an exaggerated peak ESBP response at baseline presented high resting SBP ( $\geq 140$  mmHg) 5 years later. However according to the binary logistic regression, exaggerated peak ESBP response was not a significant predictor of future resting hypertension (OR: 2.96, CI 95% [0.48 – 18.12; P = 0.24]) (Table 3).

## DISCUSSION

Hypertension is one of the most prevalent CVD and the least diagnosed in clinical setting because patients are asymptomatic most of the times<sup>5</sup>. Exaggerated peak ESBP and /or peak EDPB response have been previously suggested to be a predictor of a future resting HT as well as an early signs of future CVD in normotensive men and women<sup>10,22,23</sup>. In this study, as previously mentioned, none of the women presented an exaggerated peak EDBP. However, 15% of women at baseline and 26% at year 5 presented an exaggerated peak ESBP. Interestingly, those percentage are lower compared to the prevalence reported between 30% to 50%, in published studies<sup>6,9-11,13,24</sup>. Possible reason behind such difference in the prevalence of exaggerated peak ESBP is likely explained by study participants. More specifically these studies were cross-sectional; which included middle-aged (range: 30-66 years) men only<sup>10,11</sup>, or mostly of men<sup>6,9,13,25</sup> with an average BMI ranging between 26 kg/m<sup>2</sup> and 33 kg/m<sup>2</sup>. Only one study was done in premenopausal women<sup>13</sup>, the others have no mention on the menopausal status of the women. Furthermore, not all studies used the same criteria for exaggerated ESBP. One study used  $\geq 220$  mmHg<sup>11</sup>, while the others have used  $\geq 200$  mmHg<sup>6,10</sup> and  $\geq 230$  mmHg<sup>26</sup>. However, it should be noted that we observed a significantly higher resting systolic and diastolic BP in participants that presented an exaggerated peak ESBP response, which is consistent with our hypothesis and results reported in literature<sup>6,8,10,11</sup>. Out of those that presented an exaggerated peak ESBP response at baseline, 2 participants (14%) presented resting HT (SBP  $\geq 140$  mmHg) 5 years later. Yet, baseline peak ESBP was not a significant predictor of future resting hypertension, nor was it a significant predictor of pre-hypertension<sup>3</sup> (data not shown). Previous studies have shown that within a 5-year follow-up at least 33% of patients with an exaggerated peak EBP

response developed resting HT<sup>10,26</sup>. However, the latter studies were performed mostly in men and using different cut-offs for exaggerated peak ESBP response, where one defined peak ESBP as  $\geq 200$  mmHg<sup>10</sup>, and the other  $\geq 230$  mmHg<sup>26</sup>. Whereas, in our study the cut-off value for an exaggerated peak ESBP was  $\geq 190$  mmHg, has previously used in the Framingham study<sup>7-9</sup>. Furthermore, at baseline our sample was specifically composed of healthy and fit normotensive premenopausal women followed for 5 years.

Our results also revealed higher fasting plasma glucose levels in women displaying an exaggerated peak ESBP response. High plasma glucose was previously reported to be correlated with elevated BP<sup>27</sup>, a relationship which might be mediated by hyperinsulinemia<sup>28</sup> and/or insulin resistance<sup>13,29</sup>. The results of our study, up against literature data, showed that despite the fact that fasting glucose was significantly higher in participants with an exaggerated peak ESBP response, fasting insulin values as well as HOMA-IR index were not significantly different than those with a normal ESBP. Furthermore, BMI, waist circumference, body composition indices and trunk fat mass were not significantly higher among participants with exaggerated peak ESBP responses; which is the opposite of what was previously reported<sup>9,11-13,16</sup>. These observations can be partly explained by the normal values of fasting plasma glucose; which are in the normal glucose tolerance category. Moreover, our participants were leaner compared to previous studies<sup>9,11-13,16</sup>, based on our cohort's BMI. Also the participants' baseline mean WC value is lower ( $78.0 \pm 6.6$  cm) than the reported thresholds of 88.0 cm; which has been associated with an increased risk of cardiometabolic disturbance in women<sup>30</sup>.

Our study presents certain limitations. First the population consisted of healthy fit middle-aged women with a BMI  $< 30$  kg/m<sup>2</sup>. Therefore our findings cannot be generalized to the

whole population. Second, only a small number of participants presented an exaggerated peak ESBP response, while none presented an exaggerated peak EDBP. Third, the small number of women who became hypertensive in follow-up was very low; which most likely decreased statistical power. Fourth, due to the duration of the study BP was not measured by the same person for all women at all time points. In fact, several studies, such as Pickering (2002), noted the importance of having a single person measuring the BP to reduce the inter-individual variation. However, BP was measured using standardized procedure<sup>31</sup> and by qualified and well trained research assistants. Finally, because we worked on a low risk group of women, the study duration might be insufficient to capture the magnitude of the risk. Despite these limitations, the well-characterized cohort of women followed for 5 years strengthens the present study. We used gold standard measures methods (DEXA) for the measurement of body composition and body fat distribution. Second, direct measurement of VO<sub>2</sub> peak is a valid and highly reproducible measure of cardiorespiratory fitness<sup>32</sup>. Finally, to the exception of age, our cohort displayed a broad range of values for the variables of interest.

## **CONCLUSION**

Ours results, despite being non significant, are of great interest because in healthy and active premenopausal women, exaggerated peak ESBP is not predictive of future hypertension after 5-years follow-up throughout menopause transition. However, future studies are needed to validate our results.

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**DECLARATION OF INTEREST**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Comparison of baseline and year 5 cardiometabolic risk factors between women's with normal and exaggerated peak exercise systolic blood pressure response.

Variables	Peak Exercise Systolic Blood Pressure				Independent Effects (P value)		
	Normal (< 190 mmHg)	Exaggerated (≥ 190 mmHg)	Normal (< 190 mmHg)	Exaggerated (≥ 190 mmHg)	Time	Peak SBP	Interaction
	Baseline		Year 5				
N	81	14	61	22			
Body mass index	23.2 ± 2.3	23.6 ± 1.7	23.4 ± 2.8	23.4 ± 2.7	NS	NS	NS
% Body fat	31.4 ± 6.7	29.6 ± 5.5	33.7 ± 7.6	31.8 ± 7.8	< 0.001	NS	NS
Fat mass(kg)	19.2 ± 5.5	17.9 ± 4.1	21.1 ± 6.4	19.1 ± 6.5	< 0.01	NS	NS
Lean body mass (kg)	38.9 ± 4.1	38.1 ± 5.1	38.1 ± 4.1	37.6 ± 3.2	NS	NS	NS
Trunk fat mass (kg)	9.3 ± 3.2	8.5 ± 2.3	9.7 ± 4.0	8.4 ± 3.4	NS	NS	NS
Waist circumference (cm)	77.8 ± 7.0	78.6 ± 5.2	78.6 ± 6.9	72.2 ± 6.7	NS	NS	NS
N	82	14	62	22			
VO <sub>2</sub> peak (ml O <sub>2</sub> kg <sup>-1</sup> min <sup>-1</sup> )	33.4 ± 6.0 <sup>a</sup>	35.3 ± 6.1	31.8 ± 5.8 <sup>b</sup>	35.1 ± 7.7 <sup>c</sup>	< 0.05	NS	NS
Resting BP (mmHg)							
systolic	114.7 ± 10.9	124.6 ± 14.1	116.6 ± 10.6	127.1 ± 10.9	NS	< 0.001	NS
diastolic	72.6 ± 7.5	77.1 ± 7.6	72.9 ± 7.1	77.6 ± 5.7	NS	< 0.01	NS
N	81	14	56	22			
Triglycerides (mmol/l)	0.88 ± 0.34	0.76 ± 0.22	0.92 ± 0.50	0.84 ± 0.35	NS	NS	NS
Total Cholesterol (mmol/l)	4.46 ± 0.70	4.40 ± 0.63	5.01 ± 0.79	4.77 ± 0.82	< 0.001	NS	NS
HDL-C (mmol/l)	1.57 ± 0.36	1.59 ± 0.34	1.77 ± 0.39	1.77 ± 0.35	< 0.001	NS	NS
LDL-C (mmol/l)	2.49 ± 0.60	2.46 ± 0.68	2.82 ± 0.60	2.62 ± 0.77	< 0.01	NS	NS
TC/HDL-C	2.96 ± 0.73 <sup>d</sup>	2.87 ± 0.71	2.91 ± 0.69 <sup>e</sup>	2.80 ± 0.69	NS	NS	NS
Fasting glucose (mmol/l)	4.78 ± 0.37	5.02 ± 0.34 <sup>**</sup>	4.56 ± 0.41	4.63 ± 0.32	< 0.001	< 0.05	NS
Fasting insulin (μU/ml)	11.97 ± 5.52 <sup>d</sup>	9.84 ± 2.31	11.19 ± 4.20 <sup>f</sup>	10.20 ± 2.17 <sup>g</sup>	NS	NS	NS
HOMA-IR	2.56 ± 1.30 <sup>h</sup>	2.21 ± 0.57	2.35 ± 0.96 <sup>e</sup>	2.13 ± 0.53 <sup>g</sup>	NS	NS	NS

\*\* P ≤ 0.01; \* P ≤ 0.05.

Values are mean ± standard deviation. N: number of subjects; HDL-C: high-density-lipoproteins cholesterol; HOMA-IR: homeostasis model assessment; LDL-C: low-density-lipoproteins cholesterol; TC: total cholesterol; VO<sub>2</sub> peak: peak oxygen uptake. Triglycerides values were log-converted for statistical analysis and reconverted for presentation in table format.

<sup>a</sup> N = 81; <sup>b</sup> N = 59; <sup>c</sup> N = 20; <sup>d</sup> N = 80; <sup>e</sup> N = 52; <sup>f</sup> N = 57; <sup>g</sup> N = 21; <sup>h</sup> N = 79.

Linear mixed model repeated measures: Independent effect of time (within subject factor); Independent effect of peak systolic blood pressure (between subject factor).

Table 2. Pearson correlations between baseline peak exercise blood pressure and anthropometric and cardiometabolic indices.

	Peak exercise systolic BP	Peak exercise diastolic BP
Weight	-0.02	0.03
Body mass index	0.05	0.17
% Body Fat	-0.11	0.02
Fat mass	-0.09	0.02
Lean body mass	-0.09	0.02
Trunk fat mass	-0.08	0.06
Waist circumference	-0.04	0.13
Triglycerides	-0.14	0.06
Total cholesterol	-0.15	-0.12
HDL-C	-0.07	-0.03
LDL-C	-0.09	-0.13
TC/HDL-C	-0.03	-0.04
Fasting glucose	0.17	0.16
Fasting insulin	-0.09	-0.07
HOMA-IR	-0.06	-0.06
VO <sub>2</sub> peak	0.20	0.05
Heart rate max	-0.10	0.10
Resting blood pressure		
Systolic	0.44**	0.54**
Diastolic	0.27**	0.52**

\*\*  $P \leq 0.01$ .

BP: blood pressure; VO<sub>2</sub> peak: peak oxygen uptake ( $\text{mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ); HDL-C: high-density-lipoproteins cholesterol; LDL-C: low-density-lipoproteins cholesterol; TC: total cholesterol HOMA-IR: homeostasis model assessment.

Table 3. Odds ratio associations between peak exercise systolic blood pressure (peak ESBP) response and hypertension at year 5 in women.

	Resting blood pressure		Odds Ratio	95% Confidence Interval	P Value
	Normotensive (< 140 mmHg)	Hypertensive ( $\geq$ 140 mmHg)			
Peak ESBP response					
< 190 mmHg	65	4			
$\geq$ 190 mmHg	11	2	2.96	0.48 – 18.12	0.24

Dependent variable: presence of hypertension.

**CHAPTER 7****INFLUENCE OF CARDIORESPIRATORY FITNESS AND PHYSICAL ACTIVITY  
LEVELS ON CARDIOMETABOLIC RISK FACTORS DURING MENOPAUSE  
TRANSITION: A MONET STUDY**

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Éric Doucet, Martin Brochu, Rémi Rabasa-Lhoret, Jean-Marc Lavoie and Denis Prud'homme participated in the development of the research project (MONET). Joseph Abdounour and Sahar Razmjou participated in the data collection. Joseph Abdounour and Denis Prud'homme performed the analysis and interpretation and completed the writing of the manuscript. All authors were involved in the revision and interpretation of the paper.

**Influence of Cardiorespiratory Fitness and Physical Activity Levels on  
Cardiometabolic Risk Factors during Menopause Transition: A MONET Study**

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**ABSTRACT**

**Objective:** To determine the influence of cardiorespiratory fitness (CRF) and physical activity levels on cardiometabolic risk factors in premenopausal women going through the menopause transition. **Method:** An ancillary study including 66 premenopausal women who participated to a 5-year observational, longitudinal study on the effects of menopause transition on body composition and cardiometabolic risk factors. Women underwent a graded exercise test on treadmill to measure peak oxygen uptake ( $\text{VO}_2$  peak) at year 1 and 5 and physical activity levels were measured using accelerometers. Cardiometabolic risk factors included: waist circumference, fasting plasma lipids, glucose and insulin levels, HOMA-IR score, c-reactive protein, apolipoprotein B (apoB) and resting systolic and diastolic blood pressure. **Results:** Change in CRF was not associated with changes in cardiometabolic risk factors. The changes in total physical activity levels on the other hand showed a significant negative association with plasma apoB levels. Three-way linear mixed model repeated measures, showed lower values of waist circumference, fasting triglycerides, insulin levels, HOMA-IR score, apoB and diastolic blood pressure in women with a  $\text{CRF} \geq 30.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  compared to women with a  $\text{CRF} < 30.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $P < 0.05$ ). However, only fasting triglycerides were lower in women with physical activity levels  $\geq 770.0 \text{ Kcal/day}$  ( $P < 0.05$ ). **Conclusion:** Between CRF and physical activity levels, CRF was associated with a more favorable cardiometabolic risk profile than physical activity levels in women followed for 5 years during the menopause transition.

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality among women in developed countries<sup>1</sup>. Many CVD risk factors have been identified such as abdominal obesity, physical inactivity, diabetes, hypertension and dyslipidemia<sup>1, 2</sup>. Cardiorespiratory fitness (CRF) as well as physical activity levels are important and independent predictors of CVD, cardiac events and death among symptomatic and asymptomatic women<sup>3-6</sup>.

CRF is a physiological attribute, defined by maximal oxygen uptake ( $\text{VO}_2 \text{ max}$ ) measured using a maximal exercise test<sup>7</sup>. A high CRF level estimated in metabolic equivalents (METs) has been defined as the 2 highest quintiles, which represents  $\geq 8.5$  METs for women between the ages of 50-59 years according to the Aerobics Center Longitudinal study<sup>8</sup>. Furthermore, a low CRF value ( $<8.5$  METs) was shown to be associated with a higher incidence of CVD events in men and women<sup>8</sup>. Conversely, high CRF has been found to be inversely associated with the levels of visceral fat, insulin resistance, blood lipids and blood pressure as well as with the prevalence of the metabolic syndrome<sup>9-12</sup> collectively reducing the risk of CVD.

Physical activity is defined as any body movement that increases energy expenditure, including both leisure time and non-leisure time activities<sup>13</sup>. The 2011 Canadian Physical Activity Guidelines for adults recommends at least 150 min of moderate-to-vigorous intensity of aerobic physical activity per week<sup>14</sup>. It has also been recommended to expend a minimum of 150 kcal/day or 1000 kcal/week of moderate-to-vigorous physical activity energy expenditure<sup>15</sup>. Such physical activity levels recommendations have been demonstrated to be associated with increased health benefits, by reducing the risk of cardiometabolic risk factors and CVD in men and women<sup>6, 14, 16-18</sup>.

Despite the fact that several studies having simultaneously investigated the association between CRF and physical activity levels and body composition, body fat distribution and cardiometabolic risk factors<sup>7, 17, 19-21</sup>, controversy remains. While the majority reported that CRF is more strongly associated than physical activity levels with CVD and cardiometabolic risk factors<sup>7, 17, 20, 21</sup>, one study suggested that physical activity levels is as good as CRF to predict individual health<sup>19</sup>. However, the majority of the studies used self-reported questionnaire for the assessment of physical activity levels<sup>7, 19-21</sup>. Although, self-reported physical activity may be useful for ranking physical activity levels in large epidemiological studies, it lacks precision and validity<sup>17</sup> for longitudinal and prospective studies compared to the measurement of total volume of physical activity by accelerometry<sup>22</sup>. Furthermore, accelerometer-derived physical activity measurements are more closely associated to cardiometabolic risk factors than that obtained from self-reported questionnaire<sup>22</sup>.

The evidence supporting a relationship between CRF and/or physical activity levels and CVD risk factors has been well documented in the general population. Still, it is questionable if these relationships are the same in women going through the menopause transition. First, this is a period in a woman's life that results in a progressive decrease in estrogen<sup>23</sup>, which is associated with an increase incidence and prevalence of cardiometabolic risk factors<sup>23</sup> and CVD<sup>24</sup>. Second, we have previously reported, in the same cohort, that the time spent performing light physical activity have a greater effect on adiposity during menopause transition than moderate and/or vigorous physical activity<sup>25</sup>. Third, the intensity of non-leisure time activities is lower than the relative intensity necessary to improve CRF<sup>13</sup>. Thus, the aim of the present study was to determine the influence of CRF and physical activity levels on cardiometabolic risk factors in non-obese women going through the

menopause transition. We tested the following hypothesis: CRF and physical activity levels would be related with a favourable cardiometabolic risk profile in women followed through the menopause transition.

## **METHODS**

### **Subjects**

The study includes data from healthy premenopausal women aged between 47 and 55 years who participated in a 5-year longitudinal study (MONET Study: Montreal Ottawa New Emerging Team)<sup>26</sup>. For the purpose of this secondary analysis, 66 out of the 91 participants who completed the original study were included, based on peak oxygen uptake (VO<sub>2</sub> peak) and physical activity levels value availability at years 1 and 5. However, no differences were observed for baseline characteristics (data not shown) between those who completed the study and the sub-sample of participant used in the present analysis. The participants' inclusion/exclusion criteria have been previously published<sup>26</sup>. This study was conducted according to the guidelines of the Declaration of Helsinki, and received the approval from the University of Ottawa and the Montfort Hospital Ethics committees.

### **Menopausal Status**

Menopausal status was determined yearly by self-reported questionnaire about menstrual bleeding and its regularity and follicle-stimulating hormone (FSH) levels were measured annually during the early follicular phase to verify the menopausal status as previously described<sup>26</sup>.

### **Anthropometric assessment**

Body weight and height were measured with a BWB-800AS digital scale and a Tanita HR-100 height rod, respectively (Tanita Corporation of America, Inc. Arlington Heights, IL). Body mass index (BMI) was then calculated [body weight kg/height (m<sup>2</sup>)]. Waist

circumference (mean of two measures) was determined using a Gulick tape at the mid-distance between the lowest rib and the iliac crest<sup>27</sup>. Body composition (fat mass and lean body mass) and % body fat were measured using dual-energy x-ray absorptiometry (DEXA) (GE-LUNAR Prodigy module, GE Medical Systems, Madison, Wi, USA) as previously described<sup>26</sup>.

### **Cardiorespiratory Fitness**

A graded progressive exercise test on the treadmill was performed to measure  $\text{VO}_2$  peak by indirect calorimetry. The progressive test consisted of 3-minute stages starting with a speed of 3.4 mph and a slope of 0% with an increasing workload to the point of participant exhaustion (speed increased to 4.0 mph by stage 6, 5.2 mph by stage 8 and 6.0 mph by stage 10; slope increased by 4% at every stage). Heart rate, blood pressure and the rate of perceived exertion (Borg scale)<sup>28</sup> were taken at rest and at the end of each stage during the test. Breath-by-breath samples of expired air were collected through a mouthpiece during the test, and measurements of  $\text{VO}_2$  and  $\text{VCO}_2$  were obtained using a Vmax 229 series metabolic cart (SensorMedics Corporation, Yorba Linda, CA). The indirect calorimetry unit was calibrated before each test according to the manufacturer's specifications.

After a brief warm up on the treadmill, women performed the exercise test. The test was terminated when at least 2 of the following criteria were achieved<sup>4</sup>: **1)** predicted maximal heart rate reached, **2)** respiratory quotient  $> 1.1$ , **3)**  $\text{VO}_2$  remained stable or decreased with an increase in workload, or **4)** rate of Borg-type scale reached  $\geq 19$ .  $\text{VO}_2$  peak was considered as the highest 30 seconds average  $\text{VO}_2$  reached during the test.

**Physical activity levels**

An accelerometer (Actical; Mini Mitter Co, Inc, Bend, OR) was used to measure physical activity levels in kcal/day and time spent in physical activity of various intensities (sedentary, light, moderate and vigorous) per week. Once a year, participants wore the accelerometer upon waking up and took it off just before going to bed for 7 consecutive days, as previously described<sup>26</sup>. Twenty-four hours of continuous recording was performed by the accelerometers and time spent performing sedentary exercise was also considered when participants were not wearing the device (sleep time). Daily activity levels measured via accelerometry were found to be a good predictor of energy expenditure ( $r = 0.92 - 0.97$ )<sup>29</sup>. The accelerometers used to measure physical activity energy expenditure in this study were also validated with the use of doubly labeled water measurements<sup>30</sup>.

**Resting blood pressure**

Qualified research assistants measured supine resting blood pressure manually from the left arm after participants had been resting quietly for 5 minutes using a standard stethoscope and a mercury sphygmomanometer. For this measurement, an appropriate cuff size was selected for each participant based on arm circumference. Assessment of resting blood pressure was standardized according to the American College of Sport Medicine<sup>31</sup>. SBP was considered as the first detectable Korotkoff sound (phase 1) and DBP was considered as the last detectable Korotkoff sound (phase 5)<sup>32</sup>.

### **Blood sampling**

Blood samples were taken after a 12-h overnight fast. Plasma insulin concentrations were measured in duplicate by radioimmunoassay using  $^{125}\text{I}$ -labeled human insulin and a human insulin antiserum (Millipore, St. Charles, MO, USA). Plasma glucose levels were determined using spectrophotometric analysis after conversion of glucose to glucose-6-phosphate by hexokinase (Sigma-Aldrich Canada Ltd., Oakville, ON, CAN; Fisher Scientific Limited, Nepean, ON, CAN). Insulin resistance was estimated using the homeostasis model assessment [HOMA-IR = (fasting glucose x fasting insulin)/22.5]. Total cholesterol (TC), high-density-lipoproteins cholesterol (HDL-C), and triglycerides (TG) were analyzed using the Vitros 950 immunoassay analyzer (Ortho Clinical Diagnostics, Johnson & Johnson Company, Markham, ON, CAN) at a wavelength of 540 nm. TC, HDL-C, and TG were used in the Friedewald<sup>33</sup> formula to calculate low-density-lipoproteins cholesterol (LDL-C) concentration. Serum c-reactive protein (CRP), was assessed by immunonephelometry on an Image analyzer (Beckman-Coulter, Villepinte, France) with detection limits of 0.20 mg/L. Apolipoprotein B (apoB) was assessed by immunoturbidimetry (Architect, Abbott, Rungis, France) with detection limits of 0.03 g/L. All measures of blood profile presented a coefficient of variation of less than 15%.

### **Statistical analysis**

Data are presented as means  $\pm$  standard deviation. Variables were first checked for normality. Consequently, only TG and CRP were log-transformed to normalize the distribution. ANOVA was performed to compare CRF and physical activity levels between menopause status (premenopause, perimenopause and postmenopause), for the purpose of

this analysis the database was transformed into cases as previously described<sup>26</sup>. Pearson's correlations were performed to document the associations between the changes (year 5 - baseline) in CRF, physical activity levels and the changes observed in variables of interest. Participants were divided into groups based on their VO<sub>2</sub> peak (< 30.0 vs. ≥ 30.0 mlO<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>) according to the high fitness (8.5 METs) classification for age and sex-specific estimated metabolic equivalent levels of CRF<sup>8</sup>. Furthermore, we elected to use daily total volume of physical activity levels expressed in kcal/day. The latter has shown to be a better metric than time spent in various physical activity intensities because it incorporates the full continuum of physical activity intensities<sup>22</sup>. Participants were therefore divided in two sub-group based on physical activity levels (< 770.0 vs. ≥ 770.0 kcal/day). Three-way linear mixed model repeated measures analyses were used for determination of main effects on cardiometabolic risk factors (waist circumference, fasting plasma lipids, glucose and insulin levels, HOMA-IR score, CRP, apoB and resting systolic and diastolic blood pressure). Time (baseline and year 5) was considered as a *within-subject* factor; VO<sub>2</sub> peak (low < 30.0 vs. high ≥ 30.0 mlO<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>) and physical activity levels (< 770.0 vs. ≥ 770.0 kcal/day) were considered as *between-subject* factor. Results are expressed as the mean ± standard deviation. A P value ≤ 0.05 was considered as significant. SPSS 17.0 for windows (SPSS Inc. Chicago, IL, USA) was used to perform statistical analyses.

## RESULTS

Participants' characteristics are presented in Table 1. At baseline, mean age of the participants was  $49.8 \pm 1.9$  years (range: 47 to 54 years), and % body fat was  $31.1 \pm 7.0$  (range: 18.2 to 41.7 %). The mean  $\text{VO}_2$  peak was  $33.6 \pm 6.5$  (range: 20.9 to  $52.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and daily physical activity energy expenditure levels was  $829.9 \pm 266.4$  (range: 326.3 to 1904.7 kcal/day).

To analyze the effect of menopause transition on CRF and physical activity levels, the database was transformed into cases based on menopausal status<sup>26</sup>. As a result, no significant differences were observed between menopause group (premenopause vs. perimenopause vs. postmenopause) for  $\text{VO}_2$  peak ( $33.9 \pm 6.3$  vs.  $33.9 \pm 6.1$  vs.  $32.7 \pm 6.6 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $p = 0.56$ ), and for physical activity levels ( $825.6 \pm 266.7$  vs.  $849.0 \pm 244.2$  vs.  $803.9 \pm 256.6$  kcal/day;  $p = 0.812$ ).

Pearsons' correlations between the changes (year 5 - baseline) in CRF, physical activity levels and the changes observed in cardiometabolic risk factors were performed. As a result, only the change in physical activity levels showed significant negative association with apoB ( $p < 0.05$ ). No significant correlations were observed between changes in CRF and cardiometabolic risk factors (Table 2).

Three-way linear mixed model repeated measures (Table 3) were performed to document the main effect of time (baseline and year 5), CRF, and physical activity levels on cardiometabolic risk factors, in women going through the menopause transition. A

significant effect of time was observed for various indices of cardiometabolic risk factors, indicating an overall increase over time, with the exception of fasting plasma glucose and CRP, which showed a decrease in time. Significant effect of CRF was also observed for waist circumference, fasting TG, insulin, HOMA-IR score, apoB and diastolic blood pressure. These variables were significantly lower in women with a  $\text{VO}_2$  peak  $\geq 30.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  compared to women with a  $\text{VO}_2$  peak  $< 30.0 \text{ mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Despite significant effect of physical activity levels was observed for waist circumference and TG ( $< 0.05$ ) only the TG was lower in women with physical activity levels  $\geq 770.0 \text{ kcal/day}$ . Finally, no CRF x physical activity levels interaction was observed for any variables of interest.

## DISCUSSION

The present study determined the influence of objective measures of CRF and physical activity levels on cardiometabolic risk factors in non-obese premenopausal women going through menopause transition. According to the mixed model repeated measures, we found that CRF had independent effects on measures of waist circumference, fasting TG, insulin, HOMA-IR score, apoB and diastolic blood pressure. The results showed overall lower values in women with a high CRF. Physical activity levels, on the other hand, was negatively associated with apoB, however this observation no longer remained in the repeated measures analysis. In fact, physical activity did not have an independent impact on more favourable values of cardiometabolic risk factors compared to CRF. This suggests that CRF may have greater cardioprotective effects than physical activity levels in women transitioning to menopause. These findings further support existing studies<sup>7, 17, 20, 21</sup> that reported CRF as a stronger correlate of cardiometabolic risk factors, despite the use of accelerometers in this study for the measurement of physical activity levels compared to self-reported questionnaire. One study reported, in a sample of Chinese women aged 55 to 69, that both physical activity (self-reported questionnaire) and CRF were inversely associated with the prevalence of the metabolic syndrome, adjusted for confounding variables<sup>21</sup>. However, when physical activity was further adjusted for CRF, the association with metabolic syndrome was eliminated; when CRF was adjusted for physical activity, the association remained<sup>21</sup>. Another study reported, in 53 men ( $68 \pm 9$  years) and 63 women ( $67 \pm 7$  years) that high CRF, independent of physical activity (measured by doubly labelled water and accelerometer), showed lower levels of fasting triglycerides, total cholesterol, TC/HDL-C, insulin and waist circumference ( $0.01 > P < 0.05$ )<sup>17</sup>.

Overall, the results are in line with the classical knowledge that fit individuals have better CVD risk factors profile than unfit subjects<sup>34-37</sup>. However, even if higher values of cardiometabolic risk factors were observed in our women with lower CRF, the absolute values were still within normal ranges. This can be explained by the fact that this cohort is composed of healthy non-obese women with no major cardiometabolic complications. Also the participants' mean waist circumference value is lower than the reported thresholds of 88.0 cm; which has been associated with an increased risk of cardiometabolic disturbance in women<sup>38</sup>.

Even though physical activity levels was not a better correlate of cardiometabolic risk factors, it is known to be an important determinant of CRF<sup>12</sup>. However, in the present study, we did not find a significant correlation between physical activity levels and CRF (data not shown). This supports the idea that these two phenotypes may act in an independent manner on various CVD risk factors<sup>17</sup> and could explain why we did not observe a CRF x physical activity levels interactions in the present study.

Finally, in healthy women, menopause *per se* was found to be associated with decrease in CRF through cardiopulmonary alterations affected by oestrogen deficiency and a reduced level of nitric oxide<sup>39</sup>. These alterations account partially for the impairment of endothelium-dependent vasodilation, preventing O<sub>2</sub> flow to match the increase O<sub>2</sub> requirement during exercise<sup>39</sup>. Despite what has been reported in the previous study, no effect of the menopausal status was observed for CRF in the present sub-group as well as reported by our group for the whole MONET cohort<sup>26</sup>. This is partly due to the fact that the participant remained fairly active, based on the absence of a significant change in physical activity levels between menopausal status, in this study, and during the 5 years follow-up, as reported elsewhere<sup>40</sup>.

Our study presents some limitations. First, the population studied consisted of healthy women with a BMI < 30 kg/m<sup>2</sup>. Therefore, our findings cannot be generalized to the whole population with a wide range of BMIs. Second, we used data taken from year 1 and year 5, based on CRF and physical activity levels availability. Therefore we could not account for CRF and physical activity levels at every year and between the yearly testing sessions during the 5-year follow-up. Finally, because we worked with healthy premenopausal women at low risk for CVD, the duration of the follow-up might be insufficient to capture the magnitude of the effect of menopause transition on cardiometabolic risk factors. Despite these limitations, the well-characterized cohort of women followed for 5 years strengthens the present study. We used indirect calorimetry and accelerometry, for the measurement of VO<sub>2</sub> peak and physical activity levels respectively, which are valid and highly reproducible measure of these phenotype<sup>22, 30, 41</sup>.

## **CONCLUSION**

The results of this study suggest that menopause does not have an impact on CRF and physical activity levels expressed in kcal/day in healthy women with a BMI <30.0 kg/m<sup>2</sup>. Furthermore, CRF was associated with more favorable values of cardiometabolic risk factors compared to physical activity levels in active non-obese women transitioning to menopause.

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**CONFLICT OF INTEREST**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Anthropometric and cardiometabolic characteristics of premenopausal women (n = 66) at baseline.

Variables	Mean $\pm$ SD	Minimum	Maximum
Age (yrs)	49.8 $\pm$ 1.9	47	54
Body mass index (kg/m <sup>2</sup> )	23.2 $\pm$ 2.4	19.3	28.7
% Body fat	31.1 $\pm$ 7.0	18.2	41.7
Fat mass (kg)	19.0 $\pm$ 5.6	9.6	29.9
Lean body mass (kg)	38.9 $\pm$ 3.9	31.1	47.3
Waist circumference (cm)	78.1 $\pm$ 7.1	62.2	93.7
Triglycerides (mmol/l)	0.84 $\pm$ 0.31	0.41	1.98
Total cholesterol (mmol/l)	4.39 $\pm$ 0.69	3.05	6.23
HDL-C (mmol/l)	1.53 $\pm$ 0.33	0.81	2.29
LDL-C (mmol/l)	2.47 $\pm$ 0.65	1.33	4.25
TC/HDL-C	3.01 $\pm$ 0.79	1.78	5.40
Fasting Glucose (mmol/l)	4.79 $\pm$ 0.38	3.80	5.70
Fasting Insulin (uU/ml)	11.45 $\pm$ 4.02	5.03	32.07
HOMA-IR	2.45 $\pm$ 0.90	1.14	6.98
CRP (mg/l)	1.70 $\pm$ 1.90	0.20	10.40
apoB (g/l)	0.74	0.47	1.20
VO <sub>2</sub> peak (mlO <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup> )	33.6 $\pm$ 6.5	20.9	52.0
PAEE (kcal/day)	829.9 $\pm$ 266.4	326.3	1904.7

N: number of subjects (number differ because of missing data); HDL-C: high-density lipoproteins cholesterol; LDL-C: low-density lipoproteins cholesterol; TC: total cholesterol; HOMA-IR: homeostasis model assessment-insulin resistance; CRF: cardiorespiratory fitness; PAEE: physical activity energy expenditure.

Table 2. Relationships between 5-year changes of cardiorespiratory fitness, physical activity levels and changes in cardiometabolic risk profile in women transitioning from pre to post-menopausal.

	CRF	Physical activity levels
n	57	57
Waist circumference	-0.24	-0.05
n	55	55
Triglycerides	-0.04	-0.01
Total Cholesterol	-0.13	-0.04
HDL-C	0.05	0.15
LDL-C	-0.12	-0.26
TC/HDL-C ratio	-0.16	-0.23
Fasting Glucose	-0.01	-0.02
Fasting Insulin	-0.16	-0.07
HOMA-IR	-0.15	-0.07
CRP	-0.01	-0.20
apoB	0.01	-0.38**
n	54	53
Blood pressure		
Systolic	-0.05	0.25
Diastolic	-0.03	0.19

CRF: cardiorespiratory fitness; n: Number of subjects; HDL-C: high-density lipoproteins cholesterol; LDL-C: low-density lipoproteins cholesterol; TC: total cholesterol; HOMA-IR: homeostasis model assessment-insulin resistance; CRP: c-reactive protein; apoB: apolipoprotein B. Triglycerides and CRP were log-converted for analysis.

\*\*P<0.01

Table 3. Cardiometabolic risk factors characteristics of women by time point and their baseline cardiorespiratory fitness ( $\text{mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and physical activity energy expenditure levels (kcal/day).

	CRF < 30.0		CRF $\geq$ 30.0		Physical activity levels < 770.0		Physical activity levels $\geq$ 770.0		Independent Effects (P value)		
	Mean $\pm$ SD		Mean $\pm$ SD		Mean $\pm$ SD		Mean $\pm$ SD		Time	CRF	PAEE
	Baseline	Year 5	Baseline	Year 5	Baseline	Year 5	Baseline	Year 5			
n	24	28	42	37	32	31	34	34			
Waist circumference (cm)	81.7 $\pm$ 6.6	82.5 $\pm$ 7.4	76.1 $\pm$ 6.5	74.3 $\pm$ 4.8	75.6 $\pm$ 6.9	76.4 $\pm$ 6.7	80.5 $\pm$ 6.5	79.1 $\pm$ 7.7	NS	<0.001	<0.05
n	24	27	42	34	32	30	34	31			
Triglycerides (mmol/l)	0.96 $\pm$ 0.38 <sup>a</sup>	0.94 $\pm$ 0.38 <sup>b</sup>	0.76 $\pm$ 0.24	0.85 $\pm$ 0.36	0.89 $\pm$ 0.39	1.01 $\pm$ 0.41	0.78 $\pm$ 0.20 <sup>c</sup>	0.77 $\pm$ 0.28 <sup>d</sup>	NS	<0.05	<0.05
Total cholesterol (mmol/l)	4.52 $\pm$ 0.69	5.02 $\pm$ 0.79	4.31 $\pm$ 0.69	4.87 $\pm$ 0.72	4.24 $\pm$ 0.60	4.90 $\pm$ 0.77	4.53 $\pm$ 0.76	5.98 $\pm$ 0.74	<0.001	NS	NS
HDL-C (mmol/l)	1.52 $\pm$ 0.40	1.68 $\pm$ 0.33	1.53 $\pm$ 0.29	1.73 $\pm$ 0.36	1.47 $\pm$ 0.32	1.68 $\pm$ 0.37	1.58 $\pm$ 0.34	1.74 $\pm$ 0.33	<0.001	NS	NS
LDL-C (mmol/l)	2.53 $\pm$ 0.73	2.87 $\pm$ 0.69	2.44 $\pm$ 0.61	2.75 $\pm$ 0.60	2.37 $\pm$ 0.53	2.75 $\pm$ 0.62	2.57 $\pm$ 0.74	2.85 $\pm$ 0.67	<0.001	NS	NS
TC/HDL-C	3.19 $\pm$ 1.02	3.11 $\pm$ 0.84	2.90 $\pm$ 0.60	2.90 $\pm$ 0.60	3.01 $\pm$ 0.72	3.01 $\pm$ 0.68	3.00 $\pm$ 0.85	2.97 $\pm$ 0.77	NS	NS	NS
Fasting glucose (mmol/l)	4.86 $\pm$ 0.49	4.63 $\pm$ 0.44	4.75 $\pm$ 0.31	4.55 $\pm$ 0.36	4.76 $\pm$ 0.35	4.57 $\pm$ 0.35	4.82 $\pm$ 0.42	4.60 $\pm$ 0.44	<0.001	NS	NS
Fasting insulin (uU/ml)	13.2 $\pm$ 5.0	11.8 $\pm$ 2.9	10.5 $\pm$ 2.9	10.2 $\pm$ 2.8 <sup>e</sup>	11.6 $\pm$ 5.1	10.7 $\pm$ 2.7 <sup>f</sup>	11.2 $\pm$ 2.7	11.0 $\pm$ 3.1	NS	<0.01	NS
HOMA-IR	2.86 $\pm$ 1.11	2.46 $\pm$ 0.66	2.21 $\pm$ 0.66	2.12 $\pm$ 0.55 <sup>g</sup>	2.48 $\pm$ 1.12	2.20 $\pm$ 0.47	2.42 $\pm$ 0.64	2.34 $\pm$ 0.75 <sup>d</sup>	NS	<0.01	NS
CRP (mg/l)	2.02 $\pm$ 2.01	1.47 $\pm$ 1.52 <sup>h</sup>	1.51 $\pm$ 1.83 <sup>i</sup>	0.99 $\pm$ 1.63 <sup>j</sup>	1.71 $\pm$ 1.97 <sup>k</sup>	1.35 $\pm$ 1.98 <sup>k</sup>	1.69 $\pm$ 1.86 <sup>k</sup>	1.05 $\pm$ 1.08 <sup>k</sup>	<0.01	NS	NS
apoB (g/l)	0.78 $\pm$ 0.18	0.80 $\pm$ 0.19 <sup>h</sup>	0.72 $\pm$ 0.12 <sup>i</sup>	0.71 $\pm$ 0.18 <sup>i</sup>	0.74 $\pm$ 0.13 <sup>k</sup>	0.73 $\pm$ 0.17 <sup>k</sup>	0.75 $\pm$ 0.16 <sup>k</sup>	0.76 $\pm$ 0.21 <sup>k</sup>	NS	<0.05	NS
n	24	27	42	33	32	29	34	31			
Resting blood pressure											
Systolic (mmHg)	114.4 $\pm$ 9.6	119.9 $\pm$ 12.3	116.2 $\pm$ 11.6	119.1 $\pm$ 11.5	115.3 $\pm$ 11.6	121.5 $\pm$ 12.1	115.8 $\pm$ 10.3	117.5 $\pm$ 11.3	NS	NS	NS
Diastolic (mmHg)	75.4 $\pm$ 6.2	75.3 $\pm$ 7.4	71.6 $\pm$ 7.6	73.3 $\pm$ 7.4	71.9 $\pm$ 7.8	75.6 $\pm$ 8.5	73.9 $\pm$ 6.8	73.9 $\pm$ 6.3	NS	<0.05	NS

CRF: cardiorespiratory fitness; PAEE: physical activity energy expenditure; N: number of subjects; HDL-C: high-density lipoproteins cholesterol; LDL-C: low-density lipoproteins cholesterol; TC: total cholesterol; HOMA-IR: homeostasis model assessment-insulin resistance. Body composition values were adjusted for the estimated energy balance; Cardiometabolic risk factors values were adjusted for estimated energy balance, total fat intake and total carbohydrate intake.

<sup>a</sup> n = 23; <sup>b</sup> n = 26; <sup>c</sup> n = 33; <sup>d</sup> n = 30; <sup>e</sup> n = 35; <sup>f</sup> n = 31; <sup>g</sup> n = 33; <sup>h</sup> n = 28; <sup>i</sup> n = 40; <sup>j</sup> n = 36; <sup>k</sup> n = 32.

Three-way repeated measures ANOVA: Independent effect of time (within subject factor); Independent effect of CRF (between subject factor); Independent effect of PAEE (between subject factor).

Triglyceride and CRP were log-converted for statistical analysis and reconverted for presentation in table format.

## CHAPTER 8

### CONCLUSION

Menopause transition is a critical period in a woman's life that appears to be associated with VMS, changes in body composition, body fat distribution, cardiometabolic risk profile, blood pressure, PA levels and CRF<sup>4</sup>. Considering the limited longitudinal studies directly examining these phenotype changes during menopause, there was a need to perform longitudinal investigations using gold standard methods to specifically measure body composition, body fat distribution, PA levels and CRF. The Montreal-Ottawa New Emerging Team (MONET) study was undertaken to fill in this gap in the medical literature. While several major MONET research projects were conducted, one of the major projects was a 5-year prospective, longitudinal, observational study of 102 premenopausal women between the age of 47 and 55 years at baseline. The primary objective was to examine the changes in body composition and cardiometabolic risk factors in non-obese women going through the menopause transition to establish a more thorough understanding of this physiological transition in the life of a woman. Despite the fact that women on average did not gain body weight throughout the 5-year follow-up into the menopause transition, they did increase their body fat mass and visceral fat content, suggesting that menopause could have more influence on body composition and fat distribution than weight *per se*. Yet, despite the increase in body fat and visceral fat, such changes were not associated with deterioration in cardiometabolic risk profile.

To follow-up on our primary objective, we performed various secondary data analyses on the original cohort looking at specific factors and their influence on adiposity and cardiometabolic risk profile. For instance, we compared body composition, trunk fat and

cardiometabolic risk factors between women with and without VMS. Given the well-documented preventive effect of PA on chronic disease risk, we also examined the influence of PA levels and its intensity on the prevalence of VMS. Overall, the women that reported experiencing VMS did not show higher body weight, adiposity, trunk fat or adverse cardiometabolic risk profile compared to women without VMS. Furthermore, neither PA levels nor the time spent in different intensities were associated with a lower prevalence of VMS.

We further investigated if an exaggerated peak EBP was associated with alteration of cardiometabolic risk factors and we attempted to delineate if exaggerated EBP could predict future resting HT in premenopausal women followed-up for 5 years. The results of that study demonstrated that women with an exaggerated peak ESBP did not have higher adiposity or elevated cardiometabolic risk factors, compared to women with a normal ESBP. Despite observing a higher resting systolic and diastolic BP in women, exaggerated peak ESBP was not a significant predictor for future resting HT.

Considering the importance of PA levels on adiposity, and/or CRF on cardiometabolic risk, we went on to evaluate the influence of CRF and PA levels on cardiometabolic risk factors. To this end, it was found that CRF was associated with more favorable values of cardiometabolic risk factors compared to total volume physical activity expressed in kcal/day.

What is the overall significance of the findings of these studies? In generally healthy physically active non-obese premenopausal women, the menopause transition would not necessarily have major effects on cardiometabolic risk factors even in presence of a significant increase in fat mass and visceral fat. Our results also suggest that CRF may have

greater cardioprotective effects in this cohort of women. The observed results provides novel knowledge to the actual body of literature by demystify the systematic weight gain and cardiometabolic risk factors alteration during menopause transition<sup>190</sup>. Furthermore, CRF may be used to identify women at risk of cardiometabolic alterations during menopause transition. Consequently, we suggest, based on our results, that women should be active during their daily lives, before, during and after menopause to attenuate the increase in fat gain, and also include regular exercise session to improve their CRF to prevent cardiometabolic risk factor alterations. However, high quality studies evaluating the effectiveness of interventions targeting body weight changes in women during their menopause transition are needed<sup>191</sup>.

Considering that the women did not show any cardiometabolic deteriorations, it is believed that the time spent in the postmenopausal years could be the culprit. In that sense, a longer observational period may be required for the development of comorbidities normally associated with menopause in this cohort of women. However, few studies<sup>20,105,106,192</sup> have addressed the influence of postmenopause status duration on body composition, body fat distribution and cardiometabolic risk factors using gold standard methods of measurement. Therefore, it would be of interest to recontact and invite the original participants of the MONET cohort to participate in a long-term follow-up study to investigate the effect of menopausal duration on body composition and cardiovascular risk factors. Specifically, we will be able to determine whether postmenopause duration, CRF and physical activity levels, as well as the presence, absence, and timing of VMS affect adiposity, body fat distribution and cardiometabolic risk factors.

As with all clinical research involving human subjects, it is important to discuss the strengths and limitations of the studies presented in this thesis. First, the fact that all the studies in this thesis are derived from the same group of healthy women with a BMI < 30 kg/m<sup>2</sup> (MONET) is a limitation. This suggests that our findings cannot be generalized to the whole population, especially those who may be at greater risk and with unfavorable baseline characteristics (e.g., lower fitness, higher body fat, etc.). Nonetheless, it is important to mention that 45% of the women aged between 40 to 59 years in the Canadian population present a normal BMI<sup>193</sup>. Second, the areas of abdominal fat were not measured at year 5, and only performed on a small sub-group of participants at year four (n = 20), thus the interpretation of data related to abdominal fat should be taken cautiously. With respect to statistical power, the number of women in the premenopausal group decreased throughout the study as expected, slightly reducing our ability to detect small changes in outcome variables. Finally, because we included healthy premenopausal women at low risk for CVD, the duration of the follow-up might be insufficient to capture the magnitude of the effect of menopause on adiposity and/or cardiometabolic risk factors. On the other hand, the present study is strengthened by the well-phenotyped cohort of women. We used gold standard measurement methods (DXA and CT scan) to evaluate body composition and abdominal fat. In addition, we used indirect calorimetry and accelerometry for the measurement of VO<sub>2</sub> peak and physical activity levels, respectively, which are valid and highly reproducible measure of these endpoints<sup>194-196</sup>. Finally, 96% of the women were either in transition or have become postmenopausal, with a drop-out rate of only 10% during the 5-year course of the study.

On a more personal thought, this thesis sheds tremendous light on what happens during the menopause transition in healthy, active, physically fit, non-obese women. With women going through such midlife transformation, it is more important than ever that they focus on maintaining or adopting an active lifestyle and improving CRF in order to maintain a healthy body weight and prevent risk of CVD. Yet, with our daily busy agendas and our increasing sedentary working environment, sustaining a healthy lifestyle has, for many, become a chore. At the same time, one must wonder if the emerging evidence of increased sedentary behaviour is only due to a lack of prioritization of PA over other daily chores or poor health literacy. Put differently, does the general population lack the required skills to manage their own health and take the right actions to prevent disease?

Health professionals have been especially committed to improve patient health literacy in recent years given the alarming prevalence of obesity and its associated chronic diseases in developing countries. However, there seems to be very scarce and limited literacy tools to help women manage their health throughout major transitional phases in their lives, such as the menopause transition. This manifestly highlights the difficult task for health professionals to provide efficient counselling to help women during this challenging transition period.

It is perhaps by focussing on the improvement of women health literacy, such as promoting the use of a knowledge translation tool<sup>197</sup>, that we may support premenopausal women in the decision making process to address their needs regarding body weight management during the menopause transition. Introducing such a tool to women, as well as to health professionals, may lead women to have an enhanced aptitude to maintain a

healthier lifestyle and an overall improved health. In the end, sometimes, it is not just a question of simply advocating, but also of effectively communicating!

## **CONTRIBUTIONS**

I have been part of the CIHR-MONET (Montreal Ottawa New Emerging Team) study from the start, a longitudinal study from 2004 to 2009, during my MSc and mid PhD on the effect of the menopause transition on body composition and cardiovascular risk factors. My contributions to this study were numerous and the training that I have been exposed, helped me develop and perform the following measurements: resting metabolic rate and thermic effects of food measurement (indirect calorimetry); body composition (DEXA); physical activity levels (accelerometer) and cardiorespiratory fitness testing. I participated in the annual evaluation of the subjects, data collection process, data entry, verification, analysis and interpretation. I also played an important role in the development and improvement of the MONET database. Finally, I have elaborated the secondary hypothesis in the present thesis.

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**APPENDIX A - Published papers during my PhD tenure**

**RELATIONSHIP BETWEEN THE BODY ADIPOSITY INDEX AND  
CARDIOMETABOLIC RISK FACTORS IN OBESE POSTMENOPAUSAL WOMEN**

Belinda Elisha, Rémi Rabasa-Lhoret, Virginie Messier, Joseph Abdunour, Antony D. Karelis

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Author contributions:

Belinda Elisha and Antony D. Karelis played a role in the conception/design as well as the acquisition of data. Rémi Rabasa-Lhoret, Virginie Messier, Joseph Abdunour contributed intellectually and to the writing of the final paper. All authors reviewed and approved the final version of this paper.

**CIRCULATING ENDOCANNABINOIDS IN INSULIN SENSITIVE VS. INSULIN  
RESISTANT OBESE POSTMENOPAUSAL WOMEN. A MONET GROUP STUDY**

Joseph Abdulnour, Siham Yasari, Rémi Rabasa-Lhoret, May. Faraj, Stefania Petrosino,  
Fabiana Piscitelli, Denis Prud'homme, Vincenzo Di Marzo

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Author contributions:

Joseph Abdulnour, Siham Yasari, Remi Rabasa-Lhoret, Vincenzo Di Marzo and Denis Prud'homme played a role in the conception/design as well as the acquisition of data.

Stefania Petrosino and Fabiana Piscitelli carried out the endocannabinoid measurements. All authors were involved in writing and interpreting the paper and gave final approval of the submitted and published versions.

**LIFESTYLE INTERVENTIONS TARGETING BODY WEIGHT CHANGES  
DURING THE MENOPAUSE TRANSITION: A SYSTEMATIC REVIEW**

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Stephanie Prince, Joseph Abdunour, and Denis Prud'homme

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Janet Jull coordinated the review, conducted the study screening/ selection, contributed intellectually during the study, and contributed to the writing of the final paper; Dawn Stacey and Denis Prud'homme conceived of the study, contributed intellectually during the study screening/selection, and contributed to the writing of the final paper; Sarah Beach, Stephanie Prince, and Joseph Abdunour contributed intellectually during the study screening/selection and contributed to the writing of the paper; Lee-Anne Ufholz conducted the search of the literature, contributed intellectually, and reviewed the final paper. All authors reviewed and approved the final version of this paper.

**LIGHT PHYSICAL ACTIVITY IS A BETTER DETERMINANT OF LOWER  
ADIPOSITY DURING THE MENOPAUSAL TRANSITION**

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Martin Brochu, Denis Prud'homme, Rémi Rabasa-Lhoret and Éric Doucet participated in the development of the research project (MONET). Marie-Ève Riou and Joseph Abdounour participated in the data collection. Marie-Ève Riou performed the analysis and interpretation. All authors were involved in the revision and interpretation of the paper.