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The effect of sex and menopause on carotid intima-media thickness and pulse wave velocity in morbid obesity

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Abstract

Background: Women are relatively protected from cardiovascular disease compared with men. Since morbid obesity is an independent risk factor for cardiovascular disease, the current study investigated whether the association between sex and cardiovascular risk factors and outcomes can be demonstrated in subjects suffering from morbid obesity.

Materials and methods: Two hundred subjects enrolled in a study on cardiovascular risk factors in morbid obesity underwent extensive laboratory screening, carotid intima-media thickness (cIMT) and pulse wave velocity (PWV) measurements. Gender differences were analysed using univariate and multivariable linear regression models. In addition, the effect of menopause on cIMT and PWV was analysed. Results of these models were reported as B coefficients with 95% confidence intervals.

Results: The group consisted of 52 men and 148 women, with a mean age of 41 (±11.8) years and a mean body mass index (BMI) of 42.7 (±5.2) kg/m^2. Both, cIMT and PWV were significantly higher in men than in women, although the difference in cIMT disappeared after adjustment for covariables such as waist circumference, age, high-density lipoprotein cholesterol and mean arterial pressure. PWV was associated with sex after adjustments for covariables in morbidly obese patients. Postmenopausal women had significantly increased cIMT and PWV when compared with premenopausal women.

Conclusion: Sex differences in PWV persist in subjects suffering from morbid obesity. However, no difference was found in cIMT between morbidly obese men and women after adjustment for classic cardiovascular risk factors. Premenopausal morbidly obese women are protected for cardiovascular disease when compared with postmenopausal morbidly obese women.

KEYWORDS
atherosclerosis, cardiovascular risk factors, menopause, morbid obesity, sex, sex differences

Clinical Trial Registration: Dutch Trial Register NTR5172.

1 | INTRODUCTION

Even though cardiovascular disease (CVD) is one of the major causes of death in both men and women at all ages, the prevalence in women is relatively low before menopause.[1] This prevalence approaches similar rates for men and women in their seventh decade of life. Women are relatively protected against CVD and require a heavier risk factor load before developing CVD.[2] The exact mechanism behind this remarkable sex differences in CVD is still not fully understood.[3]

Focusing on classic cardiovascular risk (CVR) factors, hypertension and smoking are more prevalent in men than in women.[1] Women have lower total cholesterol levels[4] and higher high-density lipoprotein cholesterol (HDL-C) values[1] than men. These sex differences in cardiovascular risk factors diminish after menopause.[1,2,4]

When studying outcome measures for subclinical atherosclerosis, such as common carotid artery intima-media thickness (cIMT) measurements or pulse wave velocity (PWV), previous studies showed that both cIMT[5-8] and PWV[9,10] are higher in men than in women. These sex differences also decrease after menopause.[3,5]

Obese subjects have increased levels of classic CVR factors[11-13] and higher cIMT and PWV values,[14-16] and both overall and cardiovascular mortality is higher in obese subjects.[17,18] Sex differences in cardiovascular mortality persist in different levels of overweight and obesity, although the differences may attenuate in obese individuals.[19] It is unclear whether these sex differences persist in morbidly obese subjects. The purpose of this study was to investigate sex differences in CVR factors in morbid obese subjects and to investigate differences in structural and functional outcome measures in terms of cIMT and PWV.

2 | METHODS

2.1 | Study population

This is a report from the ASSISI study. This prospective cohort study aims to investigate the effects of bariatric surgery on CVR factors in morbid obesity and comprises 200 patients, included in the study between April 2015 and April 2016. All subjects met the international criteria for bariatric surgery,[20] that is a BMI of $\geq$ 40 kg/m^2 or a BMI of $\geq$ 35 kg/m^2 and obesity-related comorbidity, aged 18 to 65 years. This obesity-related comorbidity includes hypertension, type 2 diabetes, dyslipidaemia, respiratory disease, severe joint disease and severe obesity-related psychological problems. Subjects with a previous cholecystectomy, a previous bariatric procedure, an acute inflammatory disease within 6 weeks prior to inclusion or immune-modulating medication were excluded. All data presented here are baseline data, which were collected at study entry.

The study was approved by the independent Regional Medical Ethical Committee Rotterdam (Maasstad Hospital, Rotterdam, The Netherlands, ABR no. NL47891.101.14), and all subjects gave written informed consent. The ASSISI study is registered in the Dutch Trial Register (NTR5172). Reporting of the study conforms to STROBE statement.[21]

2.2 | Definition of menopause, type 2 diabetes, hypertension and hypercholesterolaemia

Female subjects were considered postmenopausal based on a history of secondary amenorrhoea of $\geq$ 1 year.[22] Women who had previously undergone hysterectomy were excluded from the analysis in pre- and postmenopausal women.

Type 2 diabetes mellitus (T2DM) was defined as a HbA1c $\geq$ 48 mmol/mol (6.5%)[23] and/or the use of glucose-lowering medication. Hypertension was defined by a systolic blood pressure > 140 mm Hg, a diastolic blood pressure > 90 mm Hg and/or the use of antihypertensive medication.[24] Hypercholesterolaemia was defined as low-density lipoprotein cholesterol (LDL-C) levels > 2.5 mmol/L and/or the use of lipid-lowering drugs.[24]

2.3 | Baseline characteristics

Baseline characteristics were obtained during standard preoperative screening by the endocrinologist prior to bariatric surgery and included medical history and current medication profile. Smoking within 6 months prior to inclusion was considered "active smoking." Smoking before these 6 months was considered "previous smoking." Anthropometric characteristics included height, weight, waist circumference and blood pressure. The body mass index (in kg/m^2) and mean arterial pressure (MAP) were calculated.

2.4 | Laboratory measurements

Extensive preoperative laboratory testing was carried out in all participants. Freshly drawn blood was used for all clinical and haematological chemistry measurements. C-reactive protein (CRP), glucose, total cholesterol, HDL-C and triglycerides (TG) were determined using the DxC analyser (Beckman Coulter). LDL-C values were calculated using the Friedewald formula. Apo B was determined by rate nephelometry using Image analyser (Beckman Coulter). Glycated haemoglobin (HbA1c) was measured using an HPLC G8 analyser (Tosoh Bioscience).

2.5 | Carotid intima-media thickness (cIMT)

cIMT measurements were performed by one observer, according to the consensus guidelines for carotid ultrasound for

CVD risk assessment as described previously.[25] The measurements were carried out using the ART-LAB (Esaote, Italy) by a trained and experienced sonographer, who was unaware of the patient's medical history. Ultrasound scans were performed with the patients lying in a supine position with the head resting comfortably and the neck slightly hyperextended and rotated in the opposite direction of the probe. The ultrasound images were obtained from the distal 1 cm of the far wall of each common carotid artery (CCA) using B-mode ultrasound producing two echogenic lines. These lines represent the combined thickness of the intimal and medial layers of the arterial wall. Each CCA has been imaged in three different projections: CCA right side 90-120-150 and CCA left side 210-240-270 degrees. The segments were measured semi-automated in triplicate.

2.6 | Pulse wave velocity (PWV)

PWV measurements were carried out using the Mobil-O-Graph (IEM, Germany) as previously described.[26] The Mobil-O-Graph uses an inflatable cuff to measure the PWV. The cuff was placed on the patient's bare left upper arm. Cuff size was selected based on the patient's upper arm circumference. Triplicate manual measurements were performed. PWV has been calculated by the provided software and was expressed in m/s.

2.7 | Statistical analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc).

Data are given as mean ± SD. Skewed variables are given in median and interquartile range (IQR). Categorical data were described in an absolute number as well as a percentage of the total group. Differences between males and females were analysed using independent *t* tests for continuous data with normal distribution, chi-squared tests for categorical data and independent samples Mann-Whitney *U* tests for continuous data with non-normal distribution. For statistical analysis, cIMT was defined as the mean of the six individual measurements, as described above, and PWV was defined as the mean of three individual measurements. Systolic and diastolic blood pressure were integrated in the mean arterial pressure (MAP), which is the sum of 1/3 systolic blood pressure and 2/3 diastolic blood pressure.[27-29]

The associations between cIMT and PWV with sex were evaluated with univariate linear regression analysis. Since cIMT is a skewed variable logarithmic transformation was performed on this variable. Within the models, this transformed variable is named "log cIMT." The log cIMT showed a normal distribution with skewedness of 0.414 and a kurtosis of −0.329 and is thereby an appropriate dependent variable for the models. Covariables in further analyses included age, BMI, waist circumference, smoking habit, TG, HDL-C, LDL-C, CRP, HbA1c and MAP. Correlations between covariables (multicollinearity) were checked for confounding, and interaction effects were checked using stratified analysis. Within the regression model for log cIMT, a significant interaction effect was observed between HDL-C and TG, while waist circumference was a significant confounder. In the PWV model, sex and waist circumference interacted. Other confounding factors were ignored in the analyses for having a low correlation or small effect on the outcome measures. After stratification for the confounder "waist circumference," the association between log cIMT and sex was evaluated with multivariable linear regression analysis (model: backwards stepwise). The following variables were entered into the model: sex, age, BMI, waist circumference, smoking habit, TG, HDL-C, LDL-C, CRP, HbA1c, MAP and the interaction effect "HDL-C x TG." The association between PWV and sex was assessed in a multivariable linear regression analysis (model: backwards stepwise), including sex, age, BMI, waist circumference, smoking habit, TG, HDL-C, LDL-C, CRP, HbA1c, MAP and the interaction effect "sex x waist circumference."

In addition, the effect of menopausal status in women on cIMT as well as PWV was assessed using ANOVA tests and univariate and multivariable linear regression analysis (model: backwards stepwise). The relationships of cIMT and PWV with age in both premenopausal and postmenopausal women as well as men were observed using scatterplots with LOESS smooth lines ($\alpha = 0.50$). Due to high correlation with menopausal state, we eventually removed age from the models (spearman's rho 0.770, $P < 0.001$). No significant confounding factors or interaction effects were observed. The following variables were entered in both the log cIMT and PWV model: menopausal status, smoking habit, waist circumference, TG, HDL-C, LDL-C, CRP, HbA1c and MAP. Results of these models were reported as B coefficients with 95% confidence intervals.

3 | RESULTS

The total cohort included 200 subjects, 52 men and 148 women, with a mean age of 41 (±11.8) years and a mean BMI of 42.7 (±5.2) kg/m^2. Men had a significantly higher waist circumference and were more likely to suffer from T2DM and myocardial infarction. Systolic and diastolic blood pressure, HbA1c and triglyceride levels were increased in men, while HDL-C, LDL-C and CRP were significantly higher in female subjects. Details are displayed in Table 1.

The median cIMT was measured in 152 study subjects and was significantly higher in men than in women (0.638 mm (IQR 0.549-0.735) and 0.529 mm (IQR 0.478-0.600),

TABLE 1 Differences in baseline characteristics in male and female subjects and pre- and postmenopausal subjects

	Male	Female		Premenopausal	Postmenopausal	
Number	**52**	**148**	***P*-value**	**98**	**45**	***P*-value**
Age (y)	43.7 (±11.0)	40.6 (±12.0)	0.098[b]	34.1 (±9.4)	53.4 (±4.2)	<0.001[b]
Medical history (n,%)						
Diabetes mellitus type 2	18 (34.6%)	22 (14.9%)	0.002[a]	10 (10.2%)	11 (24.4%)	0.025[a]
Hypertension	22 (42.3%)	47 (31.8%)	0.169[a]	21 (21.4%)	25 (55.6%)	<0.001[a]
Hypercholesterolaemia	15 (28.8%)	43 (29.1%)	0.977[a]	18 (18.4%)	25 (55.6%)	<0.001[a]
Smoking status			0.273[a]			0.872[a]
Active smoker	14 (26.9%)	37 (25.0%)		25 (25.5%)	10 (22.2%)	
Previous smoker	20 (38.5%)	42 (28.4%)		27 (27.6%)	14 (31.1%)	
Weight (kg)	145 (±20.9)	117 (±16.2)	<0.001[b]	120 (±15.0)	113 (±18.4)	0.025[b]
Height (m)	1.82 (±0.07)	1.67 (±0.07)	<0.001[b]	1.68 (±0.07)	163 (±0.07)	<0.001[b]
BMI (kg/m^2)	43.9 (±6.5)	42.3 (±4.6)	0.100[b]	42.3 (±4.1)	42.4 (±5.5)	0.904[b]
Waist circumference (cm)	139 (±12.4)	126 (±11.5)	<0.001[b]	127 (±10)	125 (±14)	0.342[b]
Systolic blood pressure (mm Hg)	145 (±17)	137 (±19)	0.009[b]	132 (±14)	149 (±20)	<0.001[b]
Diastolic blood pressure (mm Hg)	86 (±10)	80 (±9)	<0.001[b]	78 (±9)	83 (±10)	0.002[b]
Hba1c (mmol/mol)	47 (±18)	42 (±10)	0.035[b]	40 (±7.2)	45 (±12.5)	0.005[b]
Triglycerides (mmol/L)	2.69 (1.60-3.72)	1.63 (1.10-2.17)	<0.001[c]	1.54 (1.02-2.08)	1.71 (1.27-2.27)	0.112[c]
LDL-cholesterol (mmol/L)	2.8 (±0.9)	3.2 (±1.0)	0.027[b]	3.08 (±0.90)	3.41 (±1.09)	0.072[b]
HDL cholesterol (mmol/L)	1.0 (±0.2)	1.3 (±0.3)	<0.001[b]	1.27 (±0.29)	1.40 (±0.27)	0.010[b]
Apo B (g/L)	1.12 (±0.31)	1.13 (±0.30)	0.875[b]	1.10 (±0.28)	1.20 (±0.34)	0.090[b]
Lipoprotein (a) (mg/L)	143 (45-314)	211 (85-575)	0.036[c]	220 (78-568)	187 (99-584)	0.773[c]
CRP (mg/L)	4 (2-8)	7 (4-11)	<0.001[c]	8 (4-13)	6 (3-10)	0.164[c]
Leucocytes (10^9/L)	8.4 (±2.3)	8.8 (±2.5)	0.450[b]	9.1 (±2.4)	8.2 (±2.7)	0.033[b]

[a]Chi-squared.
[b]Independent *t* test.
[c]Independent samples Mann-Whitney *U* test.

respectively, $P < 0.001$). Furthermore, median PWV was measured in 146 subjects and was also significantly higher in men in comparison with women (7.3 m/s (IQR 6.6-8.0) and 6.8 m/s (IQR 5.9-8.0), respectively, $P = 0.029$) (Figure 1).

Using univariate linear regression, female sex was associated with a decrease in log cIMT (Beta: −0.362, adjusted R^2: 0.125, $P < 0.001$). In the multiple regression analysis, after stratification for the confounder waist circumference, age, HDL-C and MAP were significant contributors to log cIMT. After adjustment for age, HDL-C and mean arterial pressure, female sex was no longer significantly associated with a lower log cIMT in subjects with a relatively low waist circumference. Within the subgroup of subjects with a waist circumference of 129 cm or higher, it appears that female sex gives a decrease of 4.7% in cIMT after adjustment for covariables. Additional data are displayed in Table 2.

In a univariate analysis, female sex was negatively associated with PWV (Beta: −0.165, adjusted R^2: 0.020, $P = 0.047$). In the multivariable analysis, age, BMI, MAP, CRP and HbA1c were significant contributors to PWV. Female sex was associated with a lower PWV, when adjusted for these variables. Based on the appearance of the interaction effect "sex x waist circumference," the effect size of female sex on PWV depended on the waist circumference. To be more precise; the advantage of women over men, in terms of PWV, diminishes with increasing waist circumference. Additional data are displayed in Table 3.

Among women, there was a non-linear relation between age and both cIMT and PWV with an increased inclination of the LOESS smooth line from an age of approximately 45 years, while this relation in men appeared to be more or less linear (Figure 1). The female group consisted of 98

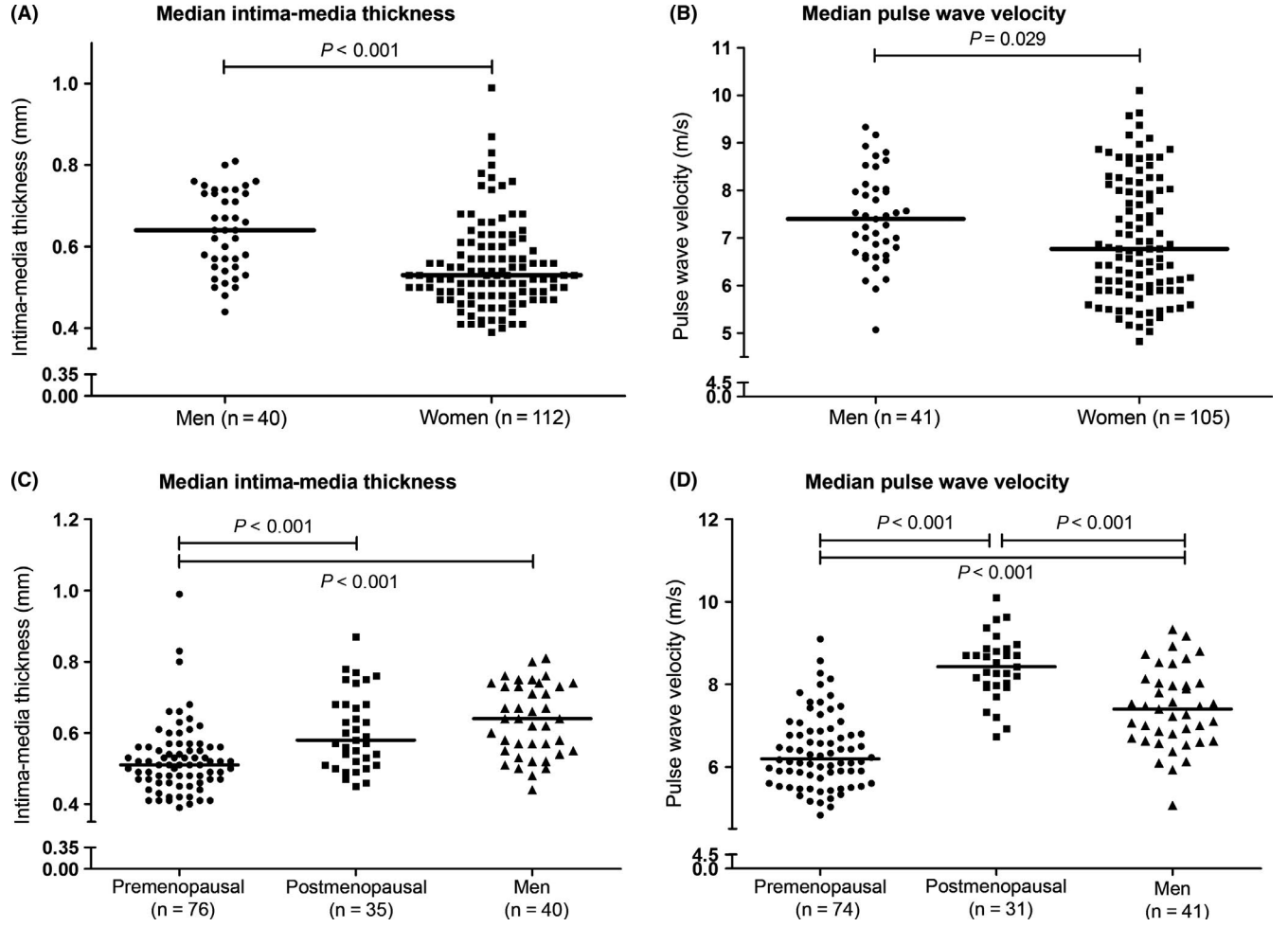

FIGURE 1 Differences in median cIMT and PWV in women versus men (a + b) and in pre- and postmenopausal women versus men (c + d)

premenopausal and 45 postmenopausal women. Five women were excluded from further analyses, due to a history of hysterectomy. Postmenopausal women were significantly more likely to suffer from comorbidities such as T2DM, hypertension and hypercholesterolaemia. Systolic and diastolic blood pressure, HbA1c and HDL-C were significantly higher in postmenopausal women, than in premenopausal women (Table 1).

Median cIMT was significantly higher in postmenopausal women, when compared with premenopausal women (0.591 mm (IQR 0.517-0.684)) and 0.512 mm (IQR 0.465-0.563), respectively, $P < 0.001$). Additionally, PWV was also significantly higher in postmenopausal women than in premenopausal women (8.5 m/s (IQR 8.0-8.8) and 6.2 m/s (IQR 5.6-6.9), respectively, $P < 0.001$). Even though no significant differences were observed in cIMT between men and postmenopausal women, PWV was significantly higher in the postmenopausal women than in men (Figure 1).

Postmenopausal state was associated with a higher log cIMT in univariate analysis (Beta: 0.363, adjusted R^2: 0.124, $P < 0.001$) as well as after adjustment for covariables (Table 4).

Menopausal status was also positively associated with PWV in both univariate linear regression model (Beta: 2.067, adjusted R^2: 0.542, $P < 0.001$) and a multivariable regression analysis (Table 4).

4 | DISCUSSION

Sex differences in CVR factors and outcome measures for subclinical atherosclerosis do not only exist in lean and overweight subjects, but persist in subjects with obesity and morbid obesity. Even though obesity is associated with an increased risk of cardiovascular disease and mortality, morbidly obese women are still relatively protected in comparison to men. However, as previously seen in lean and obese women, this advantage appears to diminish in postmenopausal morbidly obese women.

The sex differences in classic CVR factors within this study are comparable to previously described differences[1,2,4]; men had higher systolic and diastolic blood pressure and increased triglyceride levels, while women had higher HDL-C levels and higher CRP levels. In contrast

TABLE 2 Impact of sex on subclinical atherosclerosis (log cIMT)

	Log cIMT			
	Waist < 129 cm		Waist ≥ 129 cm	
Parameter	B coefficient (95% CI)	*P*-value	B coefficient (95% CI)	*P*-value
Constant	−0.340 (−0.427; −0.252)	<0.001	−0.517 (−0.660; −0.374)	<0.001
Female sex[a]	–	–	−0.047 (−0.080; −0.014)	0.006
Age	0.004 (0.002; 0.005)	<0.001	0.003 (0.002; 0.004)	<0.001
HDL cholesterol	−0.057 (−0.112; −0.001)	0.044	–	–
Mean arterial pressure	–	–	0.002 (0.000-0.003)	0.016

The impact of sex on log cIMT was evaluated with multiple linear regression analysis (backward stepwise analysis).
[a]Male subjects were scored by 0, female subjects were scored by 1.

TABLE 4 Impact of menopausal state on subclinical atherosclerosis (log cIMT and PWV)

	log cIMT			PWV	
Parameter	B coefficient (95% CI)	*P*-value	Parameter	B coefficient (95% CI)	*P*-value
Constant	−0.550 (−0.683; −0.418)	<0.001	Constant	0.983 (−0.364; 2.330)	0.151
Menopause[a]	0.037 (0.006; 0.067)	0.020	Menopause[a]	1.452 (1.132; 1.771)	<0.001
HbA1c	0.002 (0.000; 0.003)	0.035	HbA1c	0.035 (0.018; 0.052)	<0.001
MAP	0.002 (0.001; 0.003)	0.002	CRP	−0.019 (−0.038; −0.001)	0.041
HDL	–	–	MAP	0.044 (0.030; 0.057)	<0.001

The impact of menopausal state on log cIMT and PWV was evaluated with multiple linear regression analysis (backward stepwise analysis).
[a]Premenopausal women were scored by 0, postmenopausal women were scored by 1.

to previous reports,[4] women within this cohort had higher LDL-C levels in comparison with men. However, men were more likely to suffer from T2DM and the prescription of lipid-lowering drugs is part of the protocolled treatment of diabetic patients. This could explain the lower LDL-C levels in men.

Within this study, cIMT and PWV were used as outcome measures for atherosclerosis. Both measures were significantly lower in morbidly obese women in comparison with morbidly obese men, suggesting an advantage for women in terms of CVD and cardiovascular mortality. However, after adjustment for covariables, it appeared that cIMT was not so much influenced by sex, but by differences in waist circumference, age, HDL-C and MAP. Age is the main contributor to an increase in cIMT. Overall, cIMT is known to be lower in lean and overweight women, compared with men,[5-8] but this difference appears to diminish with increasing weight.[30] Unfortunately, our study only included morbidly obese subjects and no non-obese controls. No firm statements can be made on the differential effect of increasing weight on cIMT in men and women. However, obesity has been shown to affect cIMT[5,6] negatively and within lean subjects cIMT is correlated with BMI.[6] It was thought that this effect of weight on cIMT may be more profound in women than in men,[7] but our data do not support this hypothesis.

TABLE 3 Impact of sex on arterial stiffness (PWV)

	PWV	
Parameter	B coefficient (95% CI)	*P*-value
Constant	−0.005 (−1.094; 1.084)	0.993
Female sex[a]	−1.242 (−2.495; 0.011)	0.052
Age	0.083 (0.074; 0.091)	<0.001
BMI	0.015 (−0.003; 0,034)	0.100
Mean arterial pressure	0.026 (0.017; 0.034)	<0.001
CRP	-0.013 (−0.027; 0.000)	0.051
HbA1c	0.009 (0.001; 0.016)	0.021
Waist × sex	0.012 (0.002; 0.021)	0.021

The impact of sex on PWV was evaluated with multiple linear regression analysis (backward stepwise analysis).
[a]Male subjects were scored by 0, female subjects were scored by 1.

In contrast to cIMT, PWV was still associated with sex after adjustments for covariables in morbidly obese patients. As previously described,[31,32] age and blood pressure were the main contributors to PWV. In addition, female sex was associated with lower PWV, although this effect also depended on waist circumference. It has been suggested that sex is a major contributor to PWV in lean and overweight subjects[33] and our data now show that this relationship persists in subjects with obesity and morbid obesity.

Women are relatively protected against CVD, but this advantage diminishes in postmenopausal women.[2,34] Hormonal

imbalances may play an important role in the development of CVD, although some hormone replacement studies do not support this hypothesis.[34] In general, premenopausal women have lower cholesterol, LDL-C, TG and apo B levels than men and higher HDL-C levels.[19] After menopause both LDL-C and total cholesterol increase,[19] where HDL-C shows a small decline.[1] In our morbidly obese population, the differences in CVR profile between pre- and postmenopausal women were small. Postmenopausal women had a significantly increased blood pressure, in agreement with the current literature,[2] but no disadvantages were seen in the lipid-associated markers. In contrast, HDL-C was actually higher in postmenopausal women in comparison with premenopausal women. Our data suggest that the difference in CVR factors between pre- and postmenopausal women attenuates in morbidly obese subjects.

Within the current study, both cIMT and PWV were significantly increased in postmenopausal women compared with premenopausal women. These relationships persisted after adjustment for covariables. In addition to menopausal status, cIMT was mainly determined by HbA1c and MAP, whereas PWV was mainly determined by HbA1c, MAP and CRP. Age and blood pressure are two of the major determinants of these cardiovascular outcome measures.[31,32] We decided to remove age from the multivariable analyses, due to the high correlation of age and menopausal status. It can be suggested that the differences in cIMT between pre- and postmenopausal women are solely explained by age differences. However, Figure 1 reveals that the effect of age on cIMT or PWV increases after an age of approximately 45 years, suggesting an effect of menopausal status on top of the effect of age. Since menopausal status was the factor of interest and since the high correlation suggests that the majority of information on age was included in the menopausal state, it seemed justified to remove age from this analysis. However, within this study we cannot differentiate the absolute effect of age and the absolute effect of menopause, which is a limitation of this study. The effect of menopausal state on PWV may be clinically relevant. However, when not considering age as a significant contributor to cIMT, being postmenopausal only increases the cIMT value with 3.7%, making the effect on cIMT rather irrelevant. Furthermore, it is important to realize that the hormonal effects of menopause may also appear in subjects suffering from hormonal disbalances due to obesity itself, such as polycystic ovary syndrome (PCOS). None of the postmenopausal women were formerly diagnosed with PCOS, and all of these women were aged 45 years or older. However, we are not informed on the effects of hormonal disbalances on cardiovascular risk factors, cIMT and PWV in the premenopausal women.

As previously mentioned, the lack of non-obese control patients is one of the limitations of this study. It was previously suggested that differences in cIMT and PWV diminish with increasing weight. With the addition of a non-obese cohort, the relation of weight with cIMT and PWV in different weight groups could have been investigated.

Another limitation of this study is the difference in baseline characteristics between men and women. Multivariable linear regression analysis was used to adjust for differences in the baseline, in order to be able to make statements on the effect of sex on cIMT and PWV. We decided to use mean arterial pressure as a marker for hypertension. Since we were not informed on the duration of hypertension and the effect of treatment within the group of subjects suffering from hypertension, the current mean arterial pressure was the most objective parameter on blood pressure effects on cIMT and PWV. Due to a small number of subjects within this cohort, no available follow-up data conclusions were drawn on surrogate outcome measures for CVD and not on real clinical outcomes such as cardiovascular events. Unfortunately, not all subjects within this study underwent cIMT or PWV measurements due to technical problems. Baseline characteristics were presented on the entire study group and not on the subgroups that underwent cIMT and PWV measurement since the entire study group was representative for the groups that underwent cIMT and PWV measurements.

In conclusion, commonly described sex differences in cardiovascular outcome measures, such as cIMT and PWV, persist in morbidly obese subjects. Differences in cIMT cannot be explained by sex alone and are mainly related to waist circumference, age, HDL-C and MAP. The advantage of women over men appears to diminish in morbidly obese women after menopause. The advantage in CVR translates into both lower cIMT and PWV values for premenopausal women. Morbidly obese women are, nevertheless, at higher risk of developing CVD then their leaner counterparts.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

SvM has a substantial contribution in the conception and design of the study, participated in analysis and interpretation of data and drafted the manuscript. LB has a substantial contribution to the conception and design of the study and revising the manuscript for intellectual content. GJvdG

participated in study conception, in delivering laboratory data and in revision of the manuscript. EB participated in the statistical analysis and in revision of the manuscript. MD and JIJ contributed to revising the manuscript for intellectual content. NvdM participated in study conception and in delivering cIMT and PWV data. GM and MCC had a substantial contribution to the conception and design of the study and revising the manuscript for intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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