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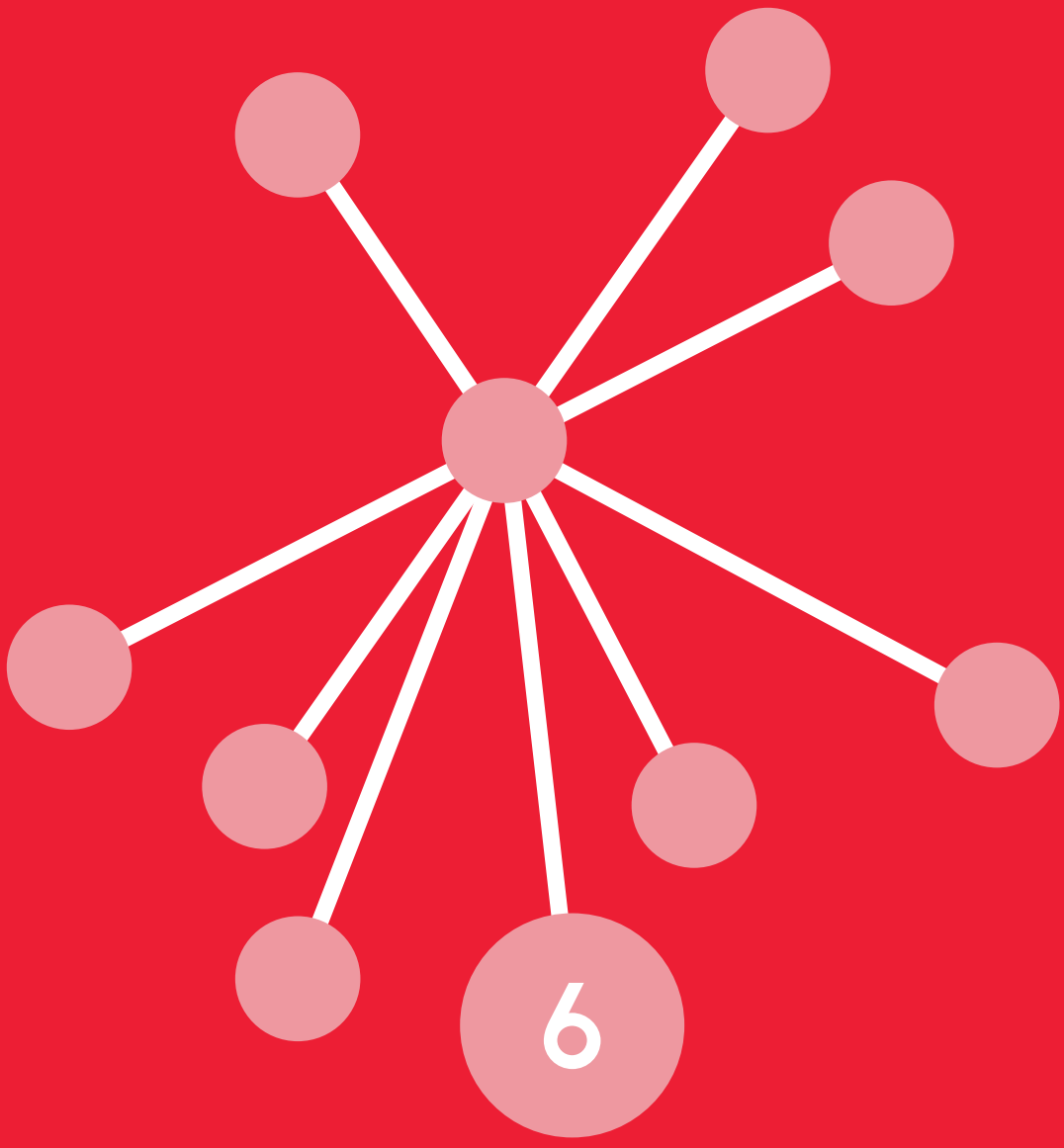
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IS EARLY MENOPAUSE A POTENTIAL CRITERION FOR CARDIOVASCULAR RISK SCREENING TO DETECT HIGH RISK IN A MULTI-ETHNIC POPULATION? THE HELIUS STUDY

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Abstract

Background

Women at risk of cardiovascular disease (CVD) may be missed with current eligibility criteria for CVD risk screening, particularly those from ethnic minority groups, among whom high risk is prevalent at a younger age. Early menopause (EM; menopause before 45 years) is associated with increased risk of CVD, and may be a potential eligibility criterion for CVD risk screening.

Aims and objectives

To determine the contribution of EM to current criteria from patient history (having a family history of CVD, current smoking, obesity and age over 50 years) for identifying women eligible for CVD risk screening in a multi-ethnic population.

Methods and results

We used baseline data (2011-2015) from 4512 women aged 45-70 years of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan ethnic origin from the HELIUS study (Amsterdam, Netherlands). Models based on current eligibility criteria with and without EM were compared on area under the curve (AUC) with regard to estimated 10-year CVD risk using the Dutch SCORE. Overall, models with EM had a higher AUC, but changes were not statistically significant. In our total sample of women aged between 45 and 70 years, the AUC changed from 0.70 (95%CI 0.69-0.72) to 0.71 (95%CI 0.69-0.72). Among women aged 45-50 years the AUC changed from 0.66 (95%CI 0.58-0.74) to 0.68 (95%CI 0.59-0.74). Results were consistent across ethnic groups.

Conclusions

The addition of EM to current eligibility criteria did not improve the detection of women at high CVD risk in a multi-ethnic sample of women aged 45-70 years.

Introduction

Cardiovascular disease (CVD) is a leading cause of death in women worldwide, representing a third of total disease-related mortality (1). Women from ethnic minority groups have a greater fatal and non-fatal CVD risk compared to the majority population in high-income countries (2–4). It is estimated that 80% of this total CVD burden can be prevented through timely screening and management (4). At present, eligibility for screening is determined based on factors from patient history (family history of premature CVD (FH), smoking, obesity, age over 50 years) or the presence of one or more known clinical risk factors (high blood pressure, raised lipid levels and diabetes). A substantial proportion of women at risk may be missed using these current eligibility criteria for CVD risk screening. This may particularly affect those in high-risk ethnic minority groups in whom high CVD risk is more prevalent at a younger age (5,6).

The detection of women with high CVD risk may be improved by expanding the current eligibility criteria for CVD risk screening (4,7). The use of female-specific risk factors is advocated increasingly (8–10)women are less likely to be diagnosed appropriately, receive preventive care, or be treated aggressively for CVD. Sex differences between men and women have allowed for the identification of CVD risk factors and risk markers that are unique to women. The 2018 American Heart Association/American College of Cardiology Multi-Society cholesterol guideline and 2019 American College of Cardiology/American Heart Association guideline on the primary prevention of CVD introduced the concept of risk-enhancing factors that are specific to women and are associated with an increased risk of incident atherosclerotic CVD in women. These factors, if present, would favor more intensified lifestyle interventions and consideration of initiation or intensification of statin therapy for primary prevention to mitigate the increased risk. In this primer, we highlight sex-specific CVD risk factors in women, stress the importance of eliciting a thorough obstetrical and gynecological history during cardiovascular risk assessment, and provide a framework for how to initiate appropriate preventive measures when sex-specific risk factors are present. For instance, early menopause (EM), menopause before 45 years of age, may serve as a potential eligibility criterion. EM and CVD are thought to have shared etiological pathways, and EM may be a marker of elevated CVD related disease measures in young women (e.g., high blood pressure) (11)the specific mechanisms involved remain elusive. Moreover, whether there is a protective role of estrogens against cardiovascular disease, and specifically LVDD, continues to be controversial. Clinical and basic science have implicated activation of the renin-angiotensin-aldosterone system (RAAS.

Women from ethnic minority populations may particularly benefit from the inclusion of EM as an eligibility criterion for the screening. The mean age at menopause (AAM) is lower, and the prevalence of EM is higher in some ethnic minority groups versus the majority population (12–15). The association of EM with incident CVD and the contribution

of EM to risk prediction algorithms for incident CVD have been previously researched (16–19), and will not be the focus of this study. However, the added value of EM for identifying women with a high estimated 10-year risk of CVD, the outcome of screening, is poorly investigated. Whether EM potentially improves finding women at higher risk through screening across ethnic subpopulations in high-income countries is unknown (9).

Therefore, the aim of this study was to assess the contribution of EM to current eligibility criteria from patient history, for identifying women eligible for CVD risk screening in a 45–70 year old population of South-Asian Surinamese, African Surinamese, Turkish, Moroccan, Ghanaian and ethnic Dutch origin living in the Netherlands (Fig.1).

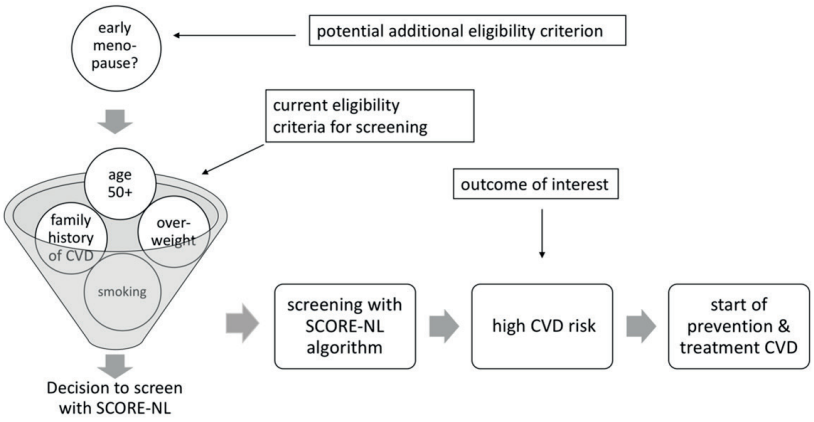

Figure 1: *This study investigated the contribution of early menopause to existing screening criteria from patient history, to predict high CVD risk. High CVD risk was defined as a 10 year risk of CVD >5% as estimated by the SCORE-NL.*

Methods

For the current study, we used baseline data from the Healthy Life in an Urban Setting (HELIUS) study conducted in Amsterdam, the Netherlands. Further details on HELIUS and the study population are described elsewhere (20) ethnic inequalities in health have been observed in relatively small studies, with limited possibilities to explore underlying causes. The aim of the Healthy Life in an Urban Setting (HELIUS. Briefly, data collection took place between 2011 and 2015. Participants between 18 and 70 years of age were randomly sampled from the municipal registry, stratified by ethnic origin. Data were collected by questionnaire, physical examination, and biological samples. In total, 22,165 participants completed both the questionnaire and the physical examination of whom 12,810 women. The HELIUS study was approved by the Institutional Review Board of the

Academic Medical Centre at the University of Amsterdam. All participants have provided written informed consent.

Definitions & measurements

AAM was measured by self-report with the question: "At what age did you first stop menstruating for 12 consecutive months?". This question is more reliable than asking a calendar year for measuring age at menopause (21). AAM was defined as the start of 12 consecutive months of amenorrhea. Classification of premature, early, normal and late AAM was done according to the Dutch primary care guideline on menopause (22). For analysis, 'premature menopause' (<40 years), and EM (40-44 years of age) were collapsed into one category, in accordance with previous studies (16,18). Thus, EM was defined as the AAM before 45 years of age.

Variables to determine eligibility for screening were based on the Dutch and EU primary care guidelines (4,7). We defined screening eligibility as fulfilling any one of the criteria from patient history (FH, current smoking, obesity, or being over 50 years old). These criteria are obtainable by clinicians before deciding to do further clinical testing which is often not indicated for younger women. FH was defined as premature CVD death or sudden death of a first-degree family member before the age of 60, according to guidelines at the time of data collection, and measured by self-report. Obesity was defined as having a body mass index (BMI) ≥30 kg/m^2 (20) ethnic inequalities in health have been observed in relatively small studies, with limited possibilities to explore underlying causes. The aim of the Healthy Life in an Urban Setting (HELIUS.

We used the Dutch SCORE (SCORE-NL) to estimate 10-year risk for both fatal and non-fatal CVD risk as described in the current Dutch primary care guideline(7), and the guidelines at the time of data collection. This algorithm estimates the 10-year risk of fatal and non-fatal CVD based on age, sex, systolic blood pressure (SBP), total cholesterol (TC)/high density lipoprotein (HDL)-ratio and smoking status. An age correction is used only in people with diabetes, making the SCORE-NL suitable for ethnic minority groups in which diabetes is highly prevalent (23). Corrected age was calculated by adding 15 years to their current age. Persons with a corrected age over 70 years (i.e., with a current age of 55 or older) were excluded, as their corrected age exceeded the 70-year upper age limit of the SCORE-NL. Measurement of SBP, TC and HDL was done as described previously (20)ethnic inequalities in health have been observed in relatively small studies, with limited possibilities to explore underlying causes. The aim of the Healthy Life in an Urban Setting (HELIUS. Current smoking status (yes/no) was measured by self-report, previous smokers were categorized as non-smokers. We classified the estimated risk derived from the SCORE-NL algorithm as low (<5%) and moderate to high (≥5%). The 5% is the threshold for a clinically relevant change in treatment approach (7).

For sensitivity analyses, blood pressure-lowering medication included centrally acting antihypertensives ATC (Anatomical Therapeutic Chemical [ATC] code C02), diuretics (C03), beta-blockers (C07), calcium channel blockers (C08) and agents acting on the renin–angiotensin–aldosterone system (C09). Glucose-lowering medication included ATC code A10. Lipid-lowering medication included ATC code C10.

Socioeconomic status (SES) was measured by self-report using the highest attained educational level (20)ethnic inequalities in health have been observed in relatively small studies, with limited possibilities to explore underlying causes. The aim of the Healthy Life in an Urban Setting (HELIUS. Levels were categorized as: (1) no or elementary schooling, (2) lower vocational or lower secondary schooling, (3) intermediate vocational, or intermediate or higher secondary schooling and (4) higher vocational schooling or university.

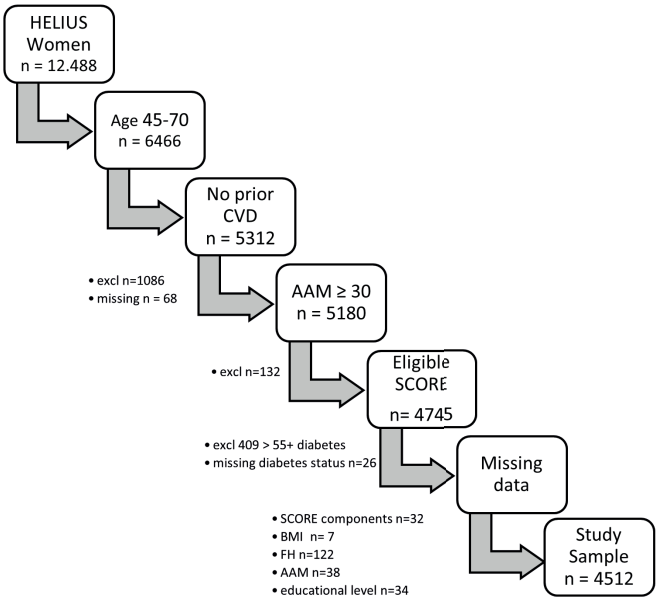

Figure 2: *Flowchart of study sample*

AAM = age at menopause; BMI = body mass index; CVD = cardiovascular disease; FH = family history of premature CVD; SCORE = Systematic COronary Risk Evaluation

Ethnicity was defined according to country of birth of the participant and that of her parents, based on the central registry of the municipality of Amsterdam. A participant was categorized in one of the ethnic groups if she, or at least one of her parents was born in the respective country (24). After data collection, Surinamese subgroups were further classified according to self-reported ethnic origin. Women from two of the four Surinamese subsamples; 'Javanese Surinamese' and 'Other Surinamese' (n=297), and

women of 'Unknown' and 'Other' ethnic origin (n=25), were excluded from the HELIUS base population due to low numbers and lack of statistical power.

Study Sample

Of the women in the HELIUS study population with complete questionnaire and physical examination (n=12,488), we first included women with a minimum age of 45 years (in whom menopause before age 45 could be confirmed) and a maximum age of 70 years based on eligibility for the SCORE-NL algorithm (n=6466; Fig.2). Next, we excluded women with a history of CVD at baseline based on self-reported prior myocardial infarction, cerebrovascular accident, angioplasty or bypass surgery on heart or legs (n=1086) or missing data on prior CVD (n=68). We excluded women with AAM below 30 years of age (n=132), because amenorrhea in these cases is often caused by underlying pathology or trauma (25). For our main analyses, we then excluded participants above 55 years of age with diabetes (n=409), or missing diabetes status (n=26).

Since all missing values were below the predefined threshold of 5% per variable and below 5% in total, we refrained from data imputation. Therefore, we excluded women with missing data on the separate components of the SCORE-NL algorithm (n=32), the criteria to define eligibility; BMI (n=7), family history of premature CVD (n=122) and AAM (n=38), or, educational level (n=34) in a final step. This resulted in a study population of n=4512 women in six ethnic subgroups: Dutch (n=1170), South-Asian Surinamese (n=635), African Surinamese (n=1135), Ghanaian (n=530), Turkish (n=469) and Moroccan (n=573).

Statistical analyses

First, distributions of baseline characteristics were checked with histograms, boxplots, qqplots, the mean and standard deviation (SD), and the Shapiro-Wilkinson test. All characteristics were non-normally distributed and reported as median (interquartile range; (IQR)). Other variables were reported as frequencies with proportions. We calculated the age-adjusted odds of EM as compared to the Dutch majority using logistic regression analyses.

Then, we used logistic regression analyses to determine the discriminative value of EM by comparing a new model with EM added, to a model with only current eligibility criteria (FH, smoking, obesity and age over 50 years), for the classification of high and low risk as estimated by the SCORE-NL. Subsequently, the area under the receiver operating characteristic curves (AUC), sensitivity, specificity, positive predictive value and negative predictive value of the models were determined. We compared the curves of the two models, with and without EM, using the DeLong method (26)DeLong's algorithm is perhaps the most widely used one due to its simplicity of implementation in practice. Unfortunately, however, the time complexity of DeLong's algorithm is of quadratic order (the product of sample sizes. For

interpretation of the AUC, we used common cut-off values: 0.5-0.6 = no discrimination, ≥0.6-<0.7 = poor, ≥0.7-<0.8 = acceptable, ≥0.8-<0.9 = excellent, ≥0.9 = outstanding (27). There are no clear cut-off values for determining a clinically relevant change in AUC. Results are shown for the whole group aged 45-70 years and for the age stratum of 45-50 (without the 'age over 50 years' criterion). We highlighted the latter group because opportunistic screening may be most relevant for the age group 45-50, as women above 50 years are recommended for systematic screening. We also stratified the analyses in the whole group for ethnicity. Because of limited events in some groups, we refrained from stratifying the analyses across ethnic groups in the age group between 45 and 50.

We performed several additional and sensitivity analyses. First, we repeated the main analysis in confirmed post-menopausal women. Pre-menopausal women (who are generally younger and therefore at lower risk of CVD compared to post-menopausal women) were included in the non-EM group in the main analyses which might lead to underestimation of risk for the total group. Second, we excluded all women with diabetes, for comparability with international SCORE algorithms that exclude people with diabetes. Third, we maximized the diabetes-corrected age of those aged above 55 years at 70 years. This differs from our main analyses where persons with diabetes of 55+ years of age are excluded, potentially disproportionately excluding people in some ethnic groups. Lastly, we analyzed the subgroup excluding women treated with blood-pressure lowering medication, cholesterol lowering medication and glucose medication because persons using these medications may have an artificially low risk.

A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using R 1.2.1335 (R Foundation for Statistical Computing, Vienna, Austria).

Results

At baseline, the median age in the study sample ranged from 50 years (IQR 47-54) for Turkish women to 56 years (IQR 50-61) for Dutch women (Table 1). Dutch women were more often highly educated compared to women in the other ethnic groups. South-Asian Surinamese women had the highest proportion of FH (55%). The proportion of smokers was lowest among Moroccan women (2%), whereas the proportion of obesity was highest among Turkish women (60%). The median estimated CVD risk was below 5% in all ethnic groups. South-Asian Surinamese women had the highest prevalence of high CVD risk (26%).

Table 1: *Characteristics of study sample*

	Total n=4512	Dutch n=1170	South Asian Surinamese n=635	African Surinamese n=1135	Ghanaian n= 530	Turkish n=469	Moroccan n=573
Median age	53 (49-58)	56 (50-61)	52 (49-57)	53 (49-58)	51 (48-54)	50 (47-54)	51 (48-56)
Age >50 years	3152 (70)	913 (78)	447 (70)	836 74	328 (62)	262 (56)	366 (64)
Educational Level							
1 No or elementary schooling	1123 (25)	45 (4)	110 (17)	53 (5)	241 (45)	282 (60)	392 (68)
2 Lower vocational or lower secondary schooling	1267 (28)	244 (21)	268 (42)	429 (38)	182 (34)	73 (16)	71 (12)
3 Intermediate vocational, or intermediate or higher secondary schooling	1029 (23)	253 (22)	149 (23)	369 (33)	98 (18)	76 (16)	84 (15)
4 Higher vocational schooling or university	1093 (24)	628 (54)	108 (17)	284 (25)	9 (2)	38 (8)	26 (5)
Median SCORE-NL	1.8 (0.8-4.3)	2.1 (0.9-4.6)	2.1 (0.9-5.2)	2.0 (1.0-4.8)	1.3 (0.8-2.9)	1.3 (0.8-3.3)	1.6 (0.7-4.2)
High CVD risk	951 (21)	260 (22)	168 (26)	268 (24)	60 (11)	80 (17)	115 (20)
Median SBP	130 (120-140)	120 (110-130)	130 (120-140)	130 (120-140)	140 (130-150)	130 (120-140)	130 (120-140)
Median TC/HDL ratio	3.3 (2.7-4.1)	3.1 (2.6-3.8)	3.6 (3-4.4)	3.2 (2.6-3.9)	3 (2.5-3.6)	3.8 (3.1-4.6)	3.5 (2.9-4.2)
BMI > 30kg/m	1622 (36)	162 (14)	149 (23)	437 (39)	284 (54)	281 (60)	309 (54)

	Total n=4512	Dutch n=1170	South Asian Surinamese n=635	African Surinamese n=1135	Ghanaian n= 530	Turkish n=469	Moroccan n=573
Smoking	723 (16)	237 (20)	114 (18)	237 (21)	17 (3)	106 (23)	12 (2)
FH	1463 (32)	364 (31)	348 (55)	354 (31)	78 (15)	199 (42)	120 (21)
Use of blood pressure-lowering medication	1080 (24)	156 (13)	154 (24)	383 (34)	218 (41)	103 (22)	66 (12)
Use of lipid-lowering medication	405 (9)	66 (6)	107 (17)	88 (8)	41 (8)	54 (12)	49 (9)
Use of glucose-lowering medication	225 (5)	2 (0)	46 (7)	55 (5)	39 (7)	35 ()	48 (8)
Diabetes	337 (7)	6 (1)	66 (10)	78 (7)	54 (10)	52 (11)	81 (14)
Post-menopausal women	2366 (52)	774 (66)	295 (46)	656 (58)	263 (50)	182 (39)	196 (34)
Median AAM	50 (45-52)	50 (48-53)	49 (46-52)	48 (44-51)	49 (45-51)	48 (45-51)	50 (46-52)
EM	10 (9-11)	8 (7-10)	8 (6-10)	15 (13-17)	9 (6-11)	9 (6-11)	6 (4-8)
Premature menopause (<40 years)	3 (2-3)	2 (1-3)	3 (1-4)	5 (4-6)	2 (1-4)	2 (1-4)	2 (1-3)
Age-standardized prevalence EM per 100 (95%CI)	10 (9-12)	9 (7-10)	10 (7-13)	15 (12-18)	16 (3-60)	9 (5-15)	7 (4-12)
OR of having EM (95%CI)	-	Reference group	1.01 (0.70-1.43)	2.00 (1.53-2.61)	1.16 (0.79-1.68)	1.13 (0.76-1.67)	0.77 (0.51-1.04)

Data is presented as median (IQR) or N (%).
SCORE = Systematic COronary Risk Evaluation, SBP = systolic blood pressure, TC/HDL ratio = total cholesterol/high density lipoprotein ratio, BMI = body mass index, FH = family history of CVD, AAM = age at menopause, EM = early menopause, OR = odds ratio, CI = confidence interval. High CVD risk is a SCORE >5%.

The Dutch group had the highest AAM and largest proportion of post-menopausal women (66%; Table 1). The overall age-adjusted prevalence of EM was 10% (95% confidence interval [CI] 9-11%), ranging from 7% (95%CI 4-12%) to 16% (95%CI 3-60%) in Moroccan and Ghanaian women, respectively. The age-adjusted odds ratios (ORs) of EM did not differ significantly in ethnic minority groups compared to the Dutch, except for African Surinamese women. The ORs for having EM ranged from 0.77 (95%CI 0.51-1.04) among Moroccan women to 2.0 (95%CI 1.53-2.61) among African Surinamese women compared to the Dutch reference group.

Overall, the model performance with current eligibility criteria was poor or borderline acceptable and improved slightly, but not statistically significantly, when EM was added as an eligibility criterion (Table 2, Table 3). For instance, in women aged 45-70 years, the AUC improved from 0.70 (95% CI 0.69-0.72) to 0.71 (95% CI 0.69-0.72) when EM was added (Supplementary Fig. 1, Table 2). Both sensitivity (94.4%) and specificity (38.7%) did not change after adding EM (Supplementary Fig. 1). In women aged 45–50 years, the AUC improved from 0.66 (95%CI 0.58-0.74) to 0.68 (CI 0.59-0.74; Supplementary Fig. 2). While the sensitivity (66.0%) did not change, specificity increased from 59.8% to 63.1% in this group. The stratified analyses across ethnic groups in women aged 45 to 70 years yielded similar patterns of small changes (Table 4).

Table 2: *Difference in performance of existing screening eligibility criteria with and without early menopause for CVD risk screening*

Main analyses	45-50 years N=1360		45-70 years N=4512	
	AUC (95%CI)	**P value**	**AUC (95%CI)**	**P value**
Current criteria: family history, smoking, obesity	0.66 (0.58-0.74)		0.57 (0.55-0.59)	
+ added EM	0.68 (0.59-0.74)	0.34	0.58 (0.56-0.60)	0.08
Current criteria: family history, smoking, obesity, age >50	x		0.70 (0.69-0.72)	
+ added EM	x		0.71 (0.69-0.72)	0.06

AUC = area under the receiving operator characteristic curve; CI= confidence interval, EM = early menopause.
** High CVD risk was defined as an estimated 10 year CVD risk > 5% according to the SCORE-NL algorithm*

Table 3: *Model specifications for eligibility criteria with and without early menopause for CVD risk screening*

Group: 45-50 years	Model 1 Current criteria		Model 2 Current criteria + early menopause	
	OR (95%CI)	**P value**	**OR (95%CI)**	**P value**
Family history of CVD	1.94 (1.09 -3.41)	0.02*	1.96 (1.11 -3.45)	0.02*
Smoking	1.28 (0.61 -2.50)	0.48	1.32 (0.63 -2.57)	0.43
Obesity	2.90 (1.66 -5.19)	<0.001*	2.95 (1.68 -5.27)	<0.001*
Early menopause	x	x	0.53 (0.13 -1.50)	0.30
Group: 45-70 years	**Model 1 Current criteria**		**Model 2 Current criteria + EM**	
	OR (95%CI)	**P value**	**OR (95%CI)**	**P value**
Family history of CVD	1.08 (0.92 -1.26)	0.36	1.07 (0.92 -1.26)	0.37
Smoking	1.54 (1.26 -1.88)	<0.001*	1.53 (1.25 -1.87)	<0.001*
Obesity	1.7 (1.50 -2.04)	<0.001*	1.74 (1.50 -2.03)	<0.001*
Age > 50	10.20 (7.74 -13.74)	<0.001*	10.18 (7.72- 13.71)	<0.001*
Early menopause	x	x	1.27 (1.01 -1.61)	0.046*

** Significant P value < 0.05*

** High CVD risk was defined as an estimated 10 year CVD risk > 5% according to the SCORE-NL algorithm*

Table 4: *Differences in area under the curve of current eligibility criteria, with and without early menopause, stratified for ethnicity, 45-70years*

	AUC existent criteria (95% CI)	AUC criteria + EM	P value
Dutch	0.70 (0.67-0.73)	0.70 (0.67-0.73)	0.98
South-Asian Surinamese	0.66 (0.62-0.71)	0.67 (0.67-0.73)	0.26
African Surinamese	0.70 (0.67-0.73)	0.70 (0.67-0.74)	0.31
Ghanaian	0.64 (0.56-0.71)	0.65 (0.57-0.72)	0.64
Turkish	0.69 (0.63-0.75)	0.69 (0.63-0.75)	0.72
Moroccan	0.73 (0.69-0.78)	0.73 (0.69-0.78)	0.44

AUC= area under the receiving operator characteristics curve; CI = confidence interval, EM = early menopause.

Finally, the results of additional and sensitivity analyses within the overall population showed similar patterns to the main analyses (Supplementary Table 1). The addition of EM was associated with small but insignificant improvements in AUC in subgroups of post-menopausal women, with people with diabetes excluded, with the diabetes-corrected-age maximized at 70 years, and in women that were currently untreated.

Discussion

The addition of EM as an eligibility criterion for CVD risk screening to existing eligibility criteria did not substantially improve the ability of these criteria to predict high estimated CVD risk, neither in women aged 45-50 years nor in the overall group aged 45-70 years. These results were similar across ethnic groups.

Limitations

Our study has limitations. First, the group of women aged under 50 years, in which results are most clinically relevant for opportunistic screening, was relatively small (n= 1082). As a consequence, we could not further stratify our analyses by ethnicity in this subgroup. Since we found that the addition of EM slightly improved current eligibility criteria in the total group of women aged 45-70 years, and this was consistent across ethnic groups, we expect no effect on our conclusions.

Second, AAM could have been reported incorrectly leading to misclassification of EM. Although self-reported AAM is considered to be a reliable measurement of AAM, there is an increasing tendency to report the perceived mean AAM of 50 years as women age (28). Consequently, older women (who by definition have a higher CVD risk) with EM could incorrectly have been classified in the not-EM group. Furthermore, we could not distinguish between natural and surgical or chemical menopause which are associated with higher CVD risk (16). Our data may underestimate the contribution of EM to current eligibility criteria in women with non-natural menopause.

Third, we used the SCORE-NL for fatal and non-fatal CVD risk as an instrument for CVD risk estimation. Other guidelines may use somewhat different criteria. For instance, the European guideline classifies people with diabetes as high CVD risk, while the SCORE-NL uses an age correction in people with diabetes. Moreover, the European guideline recommends using the algorithm based only on fatal CVD (4). Although SCORE-NL was not validated specifically within multi-ethnic populations it has been previously used. It is recommended for all groups in the current primary care guideline (7), and has been used in previous publications from our multi-ethnic population (e.g., (5)).We are uncertain whether the SCORE for fatal CVD would yield similar results. We have found no reports suggestive of a different association or predictive value of EM with only fatal CVD endpoints.

Discussion of key findings

The age-standardized prevalence of EM in our sample was higher than previously reported (10% versus 7.6%) (29)FMP <40 years. We are uncertain why our estimate is higher since there were factors that could lead to both over-estimation (different contextual factors and sample composition) and under-estimation (exclusion of women under 45). In our sample, African Surinamese women were significantly more likely to have EM compared to the Dutch subgroup. Previous studies have reported conflicting findings concerning EM in black compared to white women (12,13). Differences between black and white women, if present, were explained by differences in SES. However, even when we adjusted for SES in post-hoc analyses, African Surinamese women were more likely to have EM compared to the Dutch women (adjusted OR 1.93, 95%CI 1.47-2.55).

We found that adding EM to the current eligibility criteria did not improve identification of women with high estimated CVD risk in our study population. To our knowledge no other studies have investigated this. Interestingly, we observed that current eligibility criteria performed only borderline acceptable in our multi-ethnic sample, regardless of the addition of EM. One can question if established eligibility criteria apply equally well to ethnic subpopulations as to European host populations. For instance, the current guideline suggests to withhold CVD screening in women under 50 that have no symptoms (7). We found that all Dutch women with high CVD risk were aged over 50 in our data but, this was not observed in the ethnic minority groups who have been shown to have higher CVD risk at a younger age and may benefit from a younger age threshold (5,6).

Since the existing eligibility criteria overall performed marginally acceptable at best, we recommend future work in multi-ethnic populations, including studies focusing on ethnic minority groups, to also consider other female-specific factors, such as reproductive lifespan or parity, and psychosocial factors to improve detection of women at high CVD risk. The latter is based on the 'weathering hypothesis', which proposes that black women may age faster due to psychosocial stress (30). Although our findings seem consistent across ethnic groups, our results should be generalized to other populations and care settings with caution given possible contextual variations in underlying causes of EM and its association with CVD.

Finally, we acknowledge that our findings apply to the selection of people eligible for CVD risk screening, not to the contribution of EM for accurate risk prediction of incident CVD.

Conclusions

Our results indicate that adding EM to the current eligibility criteria for CVD risk screening does not improve the existing recommendations for determining screening eligibility

within the Dutch clinical guidelines, in a multi-ethnic population of women of 45-70 years.

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Ethical approval

The HELIUS study was approved by the Institutional Review Board of the Academic Medical Centre at the University of Amsterdam. All participants provided written informed consent.

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Supplementary Figures and Tables:

Supplementary Figure 1 & 2

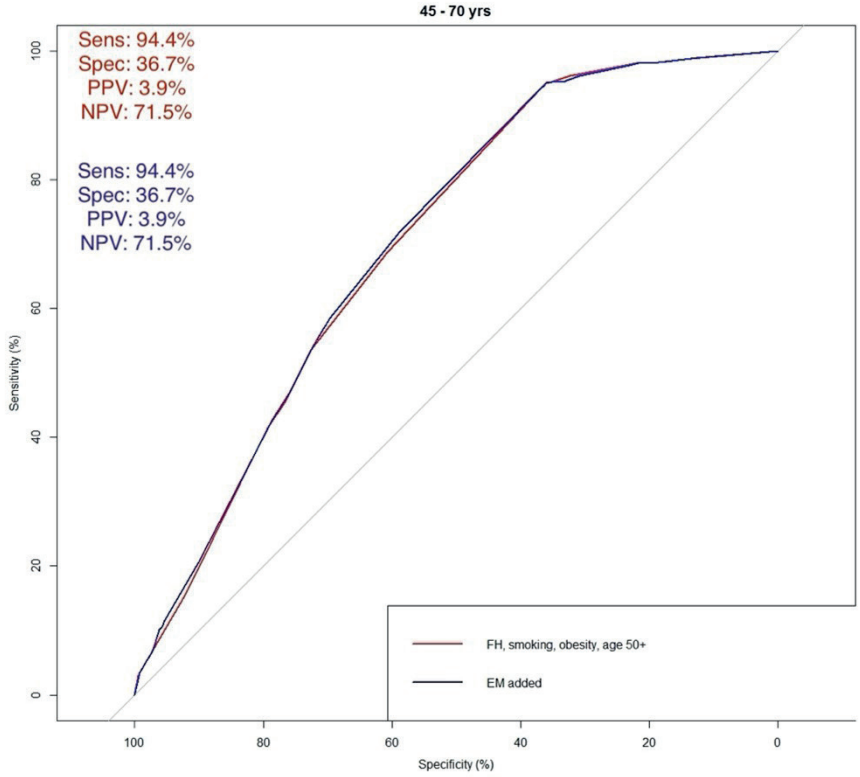

Figure 1: *family history of CVD, smoking, obesity, age over 50 with and without early menopause added, in women aged 45-70 years*

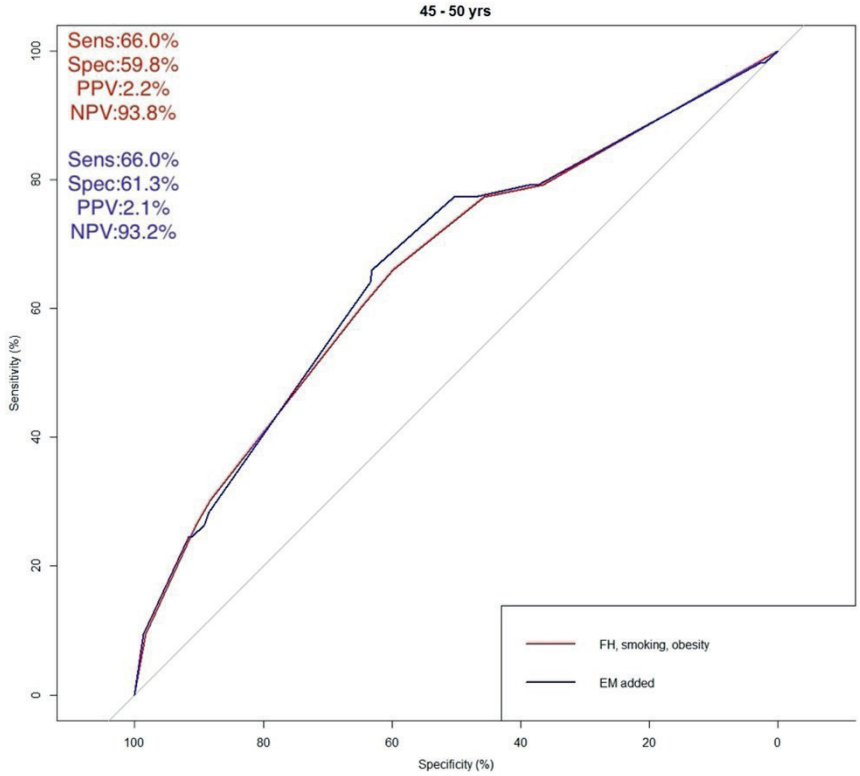

Figure 2: *family history of CVD, smoking, obesity with and without early menopause added, in women aged 45-50 years*

Supplementary Table 1: *Sensitivity analyses*

	Post-menopause[1] N=2366		Excluded diabetes[2] N=4175		Maximized diabetes[3] corrected age N=4888		Untreated[4] N=3224	
	AUC (95%CI)	**P value**	**AUC (95%CI)**	**P value**	**AUC (95%CI)**	**P value**	**AUC (95%CI)**	**P value**
Current criteria: FH, smoking, obesity	0.55 (0.53-0.58)		0.55 (0.53-0.58)		0.59 (0.57-0.61)		0.56 (0.53-0.58)	
+ added EM	0.56 (0.53-0.59)	0.07	0.56 (0.54-0.59)	0.05	0.60 (0.58-0.61)	0.02*	0.56 (0.54-0.59)	0.11
Current criteria: FH, smoking, obesity, age >50	0.60 (0.58-0.63)		0.61 (0.59-0.63)		0.72 (0.71-0.73)		0.72 (0.70-0.74)	
+ added EM	0.61 (0.59-0.64)	0.22	0.62(0.59-0.64)	0.11	0.73 (0.71-0.74)	0.03*	0.73 (0.71-0.75)	0.10

[1] Only women with confirmed self-reported menopause
[2] Exclusion of all participants with diabetes.
[3] Inclusion of all participants with diabetes, diabetes corrected age maximized at 70 years.
[4] Exclusion of participants currently treated with lipid lowering-, blood pressure lowering- or glucose lowering medication.
AUC = area under the receiving operator characteristic curve; 95%CI = 95% confidence interval; FH = family history of CVD; EM= early menopause.
For all current criteria goes that fulfilling any one of the criteria = eligible for screening
* significant P value < 0.05