Age at menarche and heart failure risk: The EPIC-NL study

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ABSTRACT (249 WORDS)

**Aims**
Early age at menarche has been associated with increased risks of developing type 2 diabetes (T2D) and coronary heart disease (CHD) in adulthood. Also a late menarche has been associated with increased risk of CHD. Both T2D and CHD are important risk factors for developing heart failure (HF). We examined the relation between age at menarche (AAM) and HF incidence in women from in the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort study.

**Methods and results**
The EPIC-NL cohort comprised of 28,504 women aged 20-70 years at baseline (1993-1997). Mean age at menarche was 13.3 (standard deviation 1.6) years. During a median follow-up of 15.2 years HF occurred in 631 women. Cox proportional hazard regression models, stratified by cohort and adjusted for potential confounders were used to investigate the associations between AAM and HF incidence. After confounder adjustment, each year later menarche was associated with 5% lower risk of HF (HR 0.95 (95% CI, 0.91-1.00), p-value 0.048). Further adjusting for either BMI, prevalent CHD, hypertension, or prevalent T2D as potential mediators between early menarche and risk of HF attenuated the associations between AAM and risk of HF to non-significance.

**Conclusion**
Later AAM reduced the risk of HF in this study. BMI, prevalent CHD, hypertension and prevalent T2D seemed to mediate this association. Future research with longer follow-up time should establish whether there is an independent effect of AAM on HF risk. Also, further phenotyping of HF cases is necessary to enable whether the associations differ for different subtypes of HF.

**Keywords**
Heart failure; Age at Menarche; Body mass index; Cohort study
Introduction

Menarche is an important event in a woman's life and is defined as the first menstrual cycle. The age at menarche (AAM) is often seen as a marker for the start of puberty in women. In previous research early menarche has shown to increase the risk of developing overweight\(^1\) and type 2 diabetes (T2D) in adulthood.\(^2\) In addition, both early- and late menarche has been associated with an increased risk of developing hypertension and coronary heart disease (CHD) in large UK studies.\(^3,4\)

Heart Failure (HF) is associated with heart damage and impairment of heart function, and it’s prevalence is estimated to be 11.8% for the population aged 60 years and older.\(^5\) The incidence rates for HF increase rapidly after the age of 69.\(^6\) Since overweight, hypertension, CHD and T2D are potential consequences of early menarche and all four are also important risk factors for developing heart failure (HF),\(^7,8\) an association of age at menarche (AAM) with HF incidence in women could be hypothesized. A systematic literature review identified shared genetic variations, based on single nucleotide polymorphisms (SNPs), between AAM and risk factors for HF.\(^9\) This review indicated a number of implicated genes related to obesity were genetically linked to AAM. These findings might consolidate the pathophysiological rational for the hypothesized association between AAM and HF, however the exact mechanism remains unclear.

The aim of the present study is to investigate whether there is an association between AAM and the risk of incident HF. Second, we aimed to assess whether overweight, hypertension, CHD and T2D mediate this association. For this purpose, we used data from a population-based cohort of over about 28,000 women, living in the Netherlands.

Methods

Participants and study design

EPIC-NL consists of the two Dutch contributions to the European Investigation Into Cancer and Nutrition (EPIC) study, the Prospect-EPIC and Morgen-EPIC cohorts. These cohorts were set up simultaneously in 1993–1997 and merged into one Dutch EPIC cohort. The design and rationale of
EPIC-NL have been described elsewhere.\textsuperscript{10} The Prospect-EPIC study includes 17,357 women aged 49–70 years living in Utrecht and vicinity.\textsuperscript{11} The MORGEN-EPIC cohort consists of 22,654 adults aged 21–64 years selected from random samples of the Dutch population in three Dutch towns.\textsuperscript{12} All participants provided informed consent before study inclusion. The study complies with the Declaration of Helsinki and was approved by the institutional board of the University Medical Center Utrecht (Prospect) and the Medical Ethical Committee of TNO Nutrition and Food Research (MORGEN). After exclusion of all men (n=10,260, 25.6%), women with prevalent HF (n=36, 0.1%) at baseline, and women who were lost to follow-up (n=1,207, 4.1%), 28,504 participants were left for analyses. Figure 1 gives a schematic overview of the in- and exclusions for our study population.

**General assessments**

At baseline, participants completed a questionnaire that included questions on date of birth, education and lifestyle, reproductive factors, risk factors for chronic diseases, and medical history. Dietary intake was assessed with a semi-quantitative validated food frequency questionnaire (FFQ). Furthermore, height, waist and hip circumference, weight, and blood pressure were measured, and a 30 ml blood sample was taken, fractionated into serum, erythrocytes and buffy coats and stored as 0.5 ml straws at -196 °C for future research.

**Assessment of age at menarche and other reproductive information**

Women reported their AAM in discrete years.

From the baseline questionnaire, we obtained information on the following reproductive risk factors: hypertension during pregnancy (yes/no/never been pregnant) and menopausal status (pre-/peri-/postmenopausal/surgically postmenopausal). Women were considered premenopausal when they reported having had regular menses over the past 12 months. Women were considered perimenopausal if they reported having had irregular menses over the past 12 months or if they indicated having had menses over the past 12 months, but were no longer menstruating at the time of enrolment. We considered women postmenopausal if they had no menses for 12 months or longer either natural or
due to surgery. Women were surgically post-menopausal if they had had a hysterectomy and/or uni- or bilateral oophorectomy before reaching natural menopause.

**Assessment of heart failure**

Hospitalization for and death from HF were used to define HF incidence. Hospitalisation for HF was determined based on both primary and secondary hospital discharge diagnoses which were obtained from the Hospital Discharge Diagnosis Register. The Hospital Discharge Diagnosis Register was linked to the EPIC-NL cohort on the basis of birth date, sex, postal code, and general practitioner by a validated probabilistic method (Herings RM 1992) and proved to be a reliable and valid source of heart failure in previous studies (Pfister R 2013). Vitality information was obtained through the municipal registry and causes of death were obtained from the Cause of Death Register at Statistics Netherlands. Death from HF was based on both primary and secondary causes of death. Hospital discharge diagnosis data were coded according to the International Classification of Diseases, Ninth Revision (ICD9), and causes of death were coded according to the International Classification of Diseases (ICD), tenth revision (ICD10). We defined incident HF as the first hospital admission with a main or sub-diagnosis of, or death caused by HF coded as ICD9 code 428/ICD10 code I50. In the Prospect cohort 512 incident HF cases have occurred versus 119 HF cases in the Morgen cohort. We were unable to subdivide HF in HF with reduced, mid-range or preserved ejection fraction.

**Assessment of other covariates**

Lifestyle factors were obtained from self-report in the baseline questionnaire. This included smoking status (never/former/current), pack years of smoking, current alcohol intake (yes/no), hypertension (yes/no) and prevalent type 2 diabetes (yes/no). Highest level of attained education was categorized in three groups, with low education defined as primary education up to lower vocational education, middle education as advanced elementary education up to higher general secretary education, and high education as higher vocational education up to university. We constructed a variable myocardial infarction (MI) prior to HF yes/no when MI (based on either self-report or the hospital discharge registry) was diagnosed before HF. Non-HDL and HDL-cholesterol were measured using
homogeneous assays with enzymatic endpoints. Systolic and diastolic blood pressures were measured in duplicate on the left arm with the subjects in sitting position after 10 minutes of rest with an automated and calibrated oscillomat (Prospect, Bosch & Son, Jungingen, Germany) or a random zero sphygmomanometer (MORGEN). Subsequently, the mean systolic and diastolic blood pressure was calculated. Body height was measured to the nearest 0.5 cm with a wall mounted stadiometer (Lameris, Utrecht, the Netherlands). Body weight was measured in light indoor clothing without shoes to the nearest 0.5 kg with a floor scale (Seca, Atlanta, GA, USA). Body mass index (BMI) was calculated as weight divided by height squared ($\text{kg/m}^2$), and treated as a continuous variable.

**Statistical analyses**

Follow-up time was defined as the time between enrolment in the cohort study and first hospital admission with a diagnosis of HF, death, loss-to follow-up or end of follow-up until January 1st, 2011. Baseline characteristics were reported as mean (SD) or median (IQR, 25th and 75th percentiles) for continuous variables and as numbers and frequencies for categorical variables, across categories of AAM ($\leq 11, 12, 13, 14, 15$ and $\geq 16$ years). Few of the women included in this study had no reported AAM ($n=523, 1.8\%$).

Missing values for variables included in the models were multiple imputed using the fully conditional specification Markov Chain Monte Carlo (MCMC) method. Predictive mean matching (PMM) was used as model type for scale variables. Imputed variables included BMI ($n=22, 0.08\%$), pack years of smoking ($n=808, 2.8\%$), alcohol status ($n=1208, 4.2\%$), education level ($n=202, 0.7\%$), categorized AAM ($n=523, 1.8\%$), HDL ($n=1536, 5.4\%$), non-HDL ($n=1541, 5.4\%$), and hypertension during pregnancy ($n=8800, 30.9\%$). Variables without missing values used to impute were: cohort, age at recruitment, menopausal status, age diagnosed with MI before diagnosed with HF, hypertension, HF survival time, HF status and prevalent type 2 diabetes, and were used as predictors only. We generated 10 complete datasets, and Rubin’s rule was used to pool the results from the datasets.\(^{14}\)

To investigate the relation between the AAM and the risk of incident HF, Cox proportional hazard regression models were built to calculate Hazard Ratios (HRs) with 95% confidence intervals per year AAM later, stratified by cohort. Follow-up time was used as time variable in the Cox
regression models. All potential confounders included in the models have been selected on basis of
differences in the variables across levels of AAM and across HF/no HF cases. Correlation coefficients
were calculated of bivariate correlations between BMI, HDL, non-HDL (Pearson) and for age at
enrolment and pack years of smoking (Spearman).

Model 1 was a Cox proportional hazards regression model, only adjusted for age at
recruitment. Model 2 additionally adjusted for pack years, alcohol status, education level, HDL and
non-HDL, the latter two treated as continuous variables. Model 3 included model 2 and additionally
adjusted for menopausal status and hypertension during pregnancy. We used regression based methods
to assess the possible intermediate roles of BMI, prevalent coronary heart disease (CHD),
hypertension and prevalent type 2 diabetes (T2D) in the association between AAM and HF [Rijnhart
2019].

Because smoking has been reported to be associated with both AAM and HF, we investigated
whether smoking is an effect modifier of the association between AAM and HF incidence by adding
the cross-product term of AAM and smoking to model 3.

Results

Overall, the median of the age at recruitment was 52.9 (IQR 46.9 - 59.1) years and the mean BMI was
25.7 (SD 4.2) kg/m². AAM ranged from 8-20 years with a mean AAM of 13.3 (SD 1.6) years.

Characteristics of the women included in this study, across categories of AAM, are described in Table
1. Those with an early AAM tended to be younger at baseline, to have a higher BMI, and to be less
physically active. Women with an early AAM also tended to smoke more, were more often
tetotallers, and suffered more often from hypertension during pregnancy. Women with earlier
menarche were also more likely to have reported diabetes during pregnancy and hyperlipidaemia.

During follow-up, in total 533 women were diagnosed with, or died of HF. The median
follow-up time was 15.2 (IQR 14.1-16.4) years.
In the age-adjusted as well as in the multivariable-adjusted models 2 and 3, each year later menarche was associated with 5% lower risk of HF (Table 2: HR\textsubscript{model 3} 0.95 (95% CI, 0.91-1.00), p-value 0.042).

When further adjusting for either BMI, prevalent CHD, hypertension, or prevalent T2D as potential mediators between early menarche and risk of HF, the associations between AAM and the risk of HF slightly attenuated and were no longer statistically significant (Table 2).

Smoking status (never/ever) did not modify the association between AAM and HF (p-value for interaction 0.28).

**Discussion**

In this large prospective study HF risk decreased by 5% per year later AAM. After adjustment for potential mediators the association attenuated with 1 to 2% depending on the mediator, and was no longer statistically significant. Even though the confidence intervals of the models with and without the mediators did overlap, this suggests that these factors may mediate the association.

This study is the first cohort study specifically addressing the association of AAM on the risk of HF. The strengths of our cohort study include its prospective design, with limited chance for selection and information bias. Potential confounders were included for adjustments in the analyses. Also mediating effects of main risk factor for HF that are known to be associated with AAM were studied.

Nevertheless, our study also had some limitations. Although our cohort has a reasonable size, the incidence of HF is still low because of the relatively young age of the participants, with a median of 52.9 (IQR 46.9 - 59.1) years. In the approximately equally sized Women’s Health Initiative Study, the number of heart failure endpoints was twice as high as in our study, with an average baseline age of the participants of 62.7 (SD 7.1) years.\textsuperscript{16}

We used hospital discharge diagnoses and causes of death registries for assessing HF. This approach will lead to detection of more severe cases, as cases that are not admitted to hospital but stay under general practitioner’s care will not be detected. Validation studies have been conducted in the
Maastricht participants of EPIC-NL and in the EPIC-Norfolk cohort (that also used hospital discharge diagnoses). They showed that the diagnosis of heart failure could be confirmed as definite or probable in 80-88% of the cases.\textsuperscript{17,18} In the Maastricht participants, the sensitivity of the diagnosis was 43%.\textsuperscript{18} This indicates that our ascertainment is a specific, but not very sensitive approach, and limits our generalizability of our study to less severe heart failure. Using the main and ten sub diagnoses, we tried to reduce the amount of this type of information bias. A study into the validity of codes used to diagnose HF in administrative data reported a misclassification of around 25% of the HF cases.\textsuperscript{19} Using broader search parameters would reduce this amount of misclassification by diagnosing more HF cases correctly and precisely. These parameters should be linked to prescribed medication and laboratory data in order to validate more HF cases.\textsuperscript{19} We were, however, unable to subdivide HF in HF with reduced, mid-range, or preserved ejection fraction.

Misclassification of self-reported AAM will probably have occurred, especially in women who were older at baseline. However, a high correlation between the original AAM and the recalled AAM after 30 years of follow-up ($r = 0.79$, $p < 0.001$) has been reported,\textsuperscript{20} indicating a relatively good validity and reproducibility of self-reported AAM. Absolute recall error seemed slightly smaller for women with an early and very late AAM.

Even though we adjusted for most potential confounders, residual confounding can never be excluded in observational research. Moreover, some of the included confounders, like blood pressure and cholesterol levels, were not measured at the actual onset of menarche but at baseline of the EPIC-NL study. This might have led to biased results of the Cox hazard regression models.

Several studies have examined the impact of an early AAM as a risk factor for a specific cardiometabolic trait or disease, in particular BMI,\textsuperscript{1,21} hypertension,\textsuperscript{4} T2D,\textsuperscript{2,22} and CHD.\textsuperscript{3,4,23} All four are also important risk factors for HF incidence.\textsuperscript{7,8} We found that adjustment for BMI, hypertension, or prevalent T2D attenuated the associations. These are all known risk factors for development of predominantly heart failure with preserved ejection fraction that is more common in women.\textsuperscript{24,25} Our results are in line with the recent findings of the Women’s Health Initiative, where the age-adjusted estimate for AAM was 0.96 (95%CI 0.93–0.99), and the multivariate-adjusted estimate was 0.98 (95% CI 0.95–1.00).\textsuperscript{16} BMI may be the causal link, since genetic variants for earlier AAM and BMI have
been reported to overlap, and BMI is itself an important risk factor for hypertension and type 2 diabetes.

Although highly speculative, several mechanisms could be responsible for an association between early menarche and risk of heart failure. A systematic review and meta-analysis showed that women with early menarche have a two times higher risk of adult obesity (Prentice P 2013). Fat cells produce the hormone resistin, which is strongly associated with risk of new onset heart failure (Butler J 2009, Frankel DS 2009). Also disturbed neurohormonal regulation may play a role, as growth hormone and testosterone have been implicated in heart failure (Arcopinto M 2015, Salzano A 2019) as well as in onset of puberty (Bordini B 2011).

In conclusion, this is the first cohort study investigating the relation between the AAM and HF incidence. Although the confidence intervals of the models with and without the potential mediators overlap, the association between timing of menarche and HF incidence seemed to be mediated by BMI, prevalent CHD, hypertension and prevalent T2D. Future studies should investigate the precise association between the AAM and the risk of HF incidence, preferably in an even larger study with a longer follow-up time, and with more precise phenotyping of HF cases, enabling the investigation of the different subtypes of HF.

**Funding statement**

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**Conflict of interest**: none declared.

**Research Data**: Data can be made available upon request

**Author contribution statement:**

Mitchell V.L. Plompen, Methodology, Software, Formal Analysis, Writing – Original Draft, Writing – Review & Editing
Yvonne T. van der Schouw, Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing – Review & Editing, Supervision, Project Administration
Frans H. Rutten, Writing – Review & Editing
W.M. Monique Verschuren, Investigation, Data Curation, Writing – Review & Editing, Project Administration
Jolanda M.A. Boer, Investigation, Data Curation, Writing – Review & Editing, Project Administration
Folkert W. Asselbergs, Writing – Review & Editing
N. Charlotte Onland-Moret: Conceptualization, Methodology, Validation, Data Curation, Writing – Review & Editing, Supervision, Project Administration
References


Table 1: Baseline characteristics of female study participants from the EPIC-NL cohort categorized by age at menarche (years)

<table>
<thead>
<tr>
<th>Variables</th>
<th>8-11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16-20</th>
<th>Overall cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3,212</td>
<td>5,883</td>
<td>7,012</td>
<td>6,044</td>
<td>3,270</td>
<td>2,560</td>
<td>28,508</td>
</tr>
<tr>
<td>Age at recruitment, median (IQR), years</td>
<td>51.5 (42.8-57.2)</td>
<td>52.3 (44.5-58.3)</td>
<td>52.0 (44.0-58.3)</td>
<td>53.1 (47.8-59.2)</td>
<td>54.5 (49.6-61.3)</td>
<td>56.8 (50.4-63.4)</td>
<td>52.9 (46.9-59.1)</td>
</tr>
<tr>
<td>Highest education*, n missing</td>
<td>9</td>
<td>17</td>
<td>23</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>202</td>
</tr>
<tr>
<td>Low education level n (%)</td>
<td>1,358 (42.4%)</td>
<td>2,304 (39.3%)</td>
<td>2,567 (36.7%)</td>
<td>2,641 (43.8%)</td>
<td>1,499 (46.0%)</td>
<td>1,338 (52.6%)</td>
<td>11,929 (41.8%)</td>
</tr>
<tr>
<td>Middle education level n (%)</td>
<td>1,333 (41.6%)</td>
<td>2,492 (42.5%)</td>
<td>2,987 (42.7%)</td>
<td>2,256 (37.4%)</td>
<td>1,213 (37.2%)</td>
<td>882 (34.6%)</td>
<td>11,304 (39.7%)</td>
</tr>
<tr>
<td>High education level n (%)</td>
<td>512 (16.0%)</td>
<td>1,070 (18.2%)</td>
<td>1,435 (20.5%)</td>
<td>1,137 (18.8%)</td>
<td>546 (16.8%)</td>
<td>326 (12.8%)</td>
<td>2,073 (7.8%)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>26.7 (4.7)</td>
<td>25.9 (4.2)</td>
<td>25.5 (4.0)</td>
<td>25.3 (4.0)</td>
<td>25.3 (4.0)</td>
<td>25.4 (4.2)</td>
<td>25.7 (4.2)</td>
</tr>
<tr>
<td>HDL-cholesterol, mean (SD), mmol/l</td>
<td>1.5 (0.4)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>Non-HDL-cholesterol, mean (SD), mmol/l</td>
<td>4.1 (1.1)</td>
<td>4.0 (1.1)</td>
<td>4.0 (1.1)</td>
<td>4.1 (1.1)</td>
<td>4.1 (1.1)</td>
<td>4.2 (1.1)</td>
<td>4.1 (1.1)</td>
</tr>
<tr>
<td>Hypertension, Yes n (%)</td>
<td>1,369 (42.6%)</td>
<td>2,385 (40.5%)</td>
<td>2,652 (37.8%)</td>
<td>2,329 (38.5%)</td>
<td>1,261 (38.6%)</td>
<td>1,054 (41.2%)</td>
<td>11,271 (39.5%)</td>
</tr>
<tr>
<td>CHD prior to HF, Yes n (%)</td>
<td>51 (1.6%)</td>
<td>92 (1.9%)</td>
<td>90 (1.3%)</td>
<td>83 (1.4%)</td>
<td>54 (1.7%)</td>
<td>62 (2.4%)</td>
<td>461 (1.6%)</td>
</tr>
<tr>
<td>T2D prior to HF, Yes n (%)</td>
<td>64 (2.0%)</td>
<td>113 (1.9%)</td>
<td>83 (1.2%)</td>
<td>100 (1.7%)</td>
<td>49 (1.5%)</td>
<td>59 (2.3%)</td>
<td>517 (1.6%)</td>
</tr>
<tr>
<td>Smoking status, n missing</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>136</td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>1,048 (32.7%)</td>
<td>1,719 (29.2%)</td>
<td>1,891 (27.0%)</td>
<td>1,592 (26.4%)</td>
<td>834 (25.5%)</td>
<td>691 (27.0%)</td>
<td>7,871 (27.6%)</td>
</tr>
<tr>
<td>In the past n (%)</td>
<td>976 (30.4%)</td>
<td>1,788 (30.4%)</td>
<td>2,257 (32.2%)</td>
<td>1,951 (32.3%)</td>
<td>1,066 (32.6%)</td>
<td>767 (30.0%)</td>
<td>8,942 (31.4%)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>1,185 (36.9%)</td>
<td>2,371 (40.3%)</td>
<td>2,859 (40.8%)</td>
<td>2,495 (41.3%)</td>
<td>1,369 (41.9%)</td>
<td>1,102 (43.0%)</td>
<td>11,559 (40.5%)</td>
</tr>
<tr>
<td>Pack years smoking*, median (IQR)</td>
<td>13.5 (5.0-24.0)</td>
<td>12.0 (4.2-21.9)</td>
<td>10.5 (3.0-21.0)</td>
<td>11.0 (3.9-21.8)</td>
<td>12.3 (4.3-23.3)</td>
<td>13.1 (4.8-23.8)</td>
<td>11.7 (4.1-22.2)</td>
</tr>
<tr>
<td>Alcohol use, n missing</td>
<td>101</td>
<td>220</td>
<td>265</td>
<td>269</td>
<td>140</td>
<td>107</td>
<td>1209</td>
</tr>
<tr>
<td>No never n (%)</td>
<td>283 (9.1%)</td>
<td>440 (7.8%)</td>
<td>532 (7.9%)</td>
<td>440 (7.6%)</td>
<td>235 (7.5%)</td>
<td>185 (7.5%)</td>
<td>2,130 (7.8%)</td>
</tr>
<tr>
<td>No, I quit n (%)</td>
<td>9 (0.7%)</td>
<td>35 (0.6%)</td>
<td>60 (0.9%)</td>
<td>35 (0.6%)</td>
<td>16 (0.5%)</td>
<td>18 (0.7%)</td>
<td>187 (0.7%)</td>
</tr>
</tbody>
</table>
Age at menarche

<table>
<thead>
<tr>
<th>Age at menarche, median (IQR) years</th>
<th>11.0 (11.0-11.0)</th>
<th>12.0 (12.0-12.0)</th>
<th>13.0 (13.0-13.0)</th>
<th>14.0 (14.0-14.0)</th>
<th>15.0 (15.0-15.0)</th>
<th>16.0 (16.0-16.0)</th>
<th>13.0 (12.0-14.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 Drink/week n (%)</td>
<td>1,146 (36.8%)</td>
<td>1,918 (33.9%)</td>
<td>2,218 (32.9%)</td>
<td>1,991 (34.5%)</td>
<td>1,067 (34.1%)</td>
<td>970 (39.5%)</td>
<td>9,498 (34.8%)</td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>1,659 (53.3%)</td>
<td>3,270 (57.7%)</td>
<td>3,938 (58.4%)</td>
<td>3,309 (57.3%)</td>
<td>1,812 (57.9%)</td>
<td>1,280 (52.2%)</td>
<td>15,481 (56.7%)</td>
</tr>
<tr>
<td>Age at menarche, median (IQR) years</td>
<td>11.0 (11.0-11.0)</td>
<td>12.0 (12.0-12.0)</td>
<td>13.0 (13.0-13.0)</td>
<td>14.0 (14.0-14.0)</td>
<td>15.0 (15.0-15.0)</td>
<td>16.0 (16.0-16.0)</td>
<td>13.0 (12.0-14.0)</td>
</tr>
<tr>
<td>Menopausal status,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal n (%)</td>
<td>1,155 (36.0%)</td>
<td>1,947 (33.1%)</td>
<td>2,447 (34.9%)</td>
<td>1,859 (30.8%)</td>
<td>872 (26.7%)</td>
<td>551 (21.5%)</td>
<td>8,886 (31.2%)</td>
</tr>
<tr>
<td>Perimenopausal n (%)</td>
<td>647 (20.1%)</td>
<td>1,072 (18.2%)</td>
<td>1,291 (18.4%)</td>
<td>1,084 (17.9%)</td>
<td>537 (16.4%)</td>
<td>390 (15.2%)</td>
<td>5,140 (18.0%)</td>
</tr>
<tr>
<td>Naturally postmenopausal n (%)</td>
<td>1,278 (39.8%)</td>
<td>2,664 (45.3%)</td>
<td>3,070 (43.8%)</td>
<td>2,903 (48.0%)</td>
<td>1,741 (53.2%)</td>
<td>1,491 (58.2%)</td>
<td>1,3472 (47.3%)</td>
</tr>
<tr>
<td>Bilateral oophorectomy n (%)</td>
<td>132 (4.1%)</td>
<td>200 (3.4%)</td>
<td>204 (2.9%)</td>
<td>198 (3.3%)</td>
<td>120 (3.7%)</td>
<td>128 (5.0%)</td>
<td>1,010 (3.5%)</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; HDL, high density lipoprotein; IQR, interquartile range; N, number; SD, standard deviation; T2D, type 2 diabetes.

a Education level was divided in three categories. Low: primary education up to lower vocational education, middle: advanced elementary education up to higher general secretary education completed and high: higher vocational education up to university completed

b Variable ‘pack years smoking’ included only women who reported to currently smoke or smoked in the past (n=16811)
<table>
<thead>
<tr>
<th>Model</th>
<th>HR per year AAM (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.95 (0.90-1.00)</td>
<td>0.056</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.95 (0.90-1.00)</td>
<td>0.038</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.95 (0.91-1.00)</td>
<td>0.042</td>
</tr>
<tr>
<td>Mediations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3 plus BMI</td>
<td>0.96 (0.91-1.01)</td>
<td>0.130</td>
</tr>
<tr>
<td>Model 3 plus prior CHD</td>
<td>0.96 (0.91-1.00)</td>
<td>0.095</td>
</tr>
<tr>
<td>Model 3 plus hypertension</td>
<td>0.96 (0.91-1.01)</td>
<td>0.100</td>
</tr>
<tr>
<td>Model 3 plus prevalent T2D</td>
<td>0.97 (0.92-1.00)</td>
<td>0.274</td>
</tr>
</tbody>
</table>

BMI, body mass index; CHD, coronary heart disease; HR, hazard ratio; IQR, interquartile range; N, number; T2D, type 2 diabetes.

Model 1: adjusted for age at recruitment.

Model 2: additionally adjusted for risk factors for HF: pack years of smoking, alcohol status (non versus drinkers), education level (low/middle/high education level), non-HDL and HDL-cholesterol.

Model 3: additionally adjusted for reproductive factor: menopausal status (pre-/peri-/postmenopausal/surgically postmenopausal).