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

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Total words count:

Target journal: European Journal of Heart Failure, ESC Heart Failure

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 in631 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.[10] The Prospect-EPIC study includes 17,357 women aged 49–70 years living in Utrecht and vicinity.[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.[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 (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 (≤11, 12, 13, 14, 15 and ≥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/m^2. 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 teetotallers, 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$_{model 3}$ 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.[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.[17,18] In the Maastricht participants, the sensitivity of the diagnosis was 43%.[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.[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.[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,[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,[1,21] hypertension,[4] T2D[2,3,22] and CHD.[3,4,23] All four are also important risk factors for HF incidence.[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.[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).[16] BMI may be the causal link, since genetic variants for earlier AAM and BMI have

been reported to overlap,[9] 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

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

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References

1.   Prentice P, Viner RM.Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis.*Int J Obes (Lond)* 2013;**37**:1036-43.

2.   Janghorbani M, Mansourian M, Hosseini E.Systematic review and meta-analysis of age at menarche and risk of type 2 diabetes.*Acta Diabetol* 2014. **51**:519-28.

3.   Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, Green J, Cairns BJ., Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort.*Circulation* 2015;**131**:237-44.

4.   Day FR, Elks CE, Murray A, Ong KK, Perry JR.Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study.*Sci Rep* 2015;**5**:11208.

5.   van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH.Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review.*Eur J Heart Fail* 2016;**18**:242-52.

6.   Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A. Deckers JW, Witteman JC, Stricker BH.Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 2004;**25**:1614-9.

7.   Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. *Am J Med* 2009;**122**:1023-8.

8.   Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P.2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC.*Eur J Heart Fail* 2016;**18**:891-975.

9.   van der Kemp J, van der Schouw YT, Asselbergs FW, Onland-Moret NC. Women-specific risk factors for heart failure: A genetic approach. Maturitas 2018;**109**:104-111.

10.   Beulens JW, Monnikhof EM, Verschuren WM, van der Schouw YT, Smit J, Ocke MC, Jansen EH, van Dieren S, Grobbee DE, Peeters PH, Bueno-de-Mesquita HB.Cohort profile: the EPIC-NL study. *Int J Epidemiol* 2010;**39**:1170-8.

11.   Boker LK, van Noord PA, van der Schouw YT, Koot NV, Bueno de Mesquita HB, Riboli E, Grobbee DE, Peeters PH.Prospect-EPIC Utrecht: study design and characteristics of the cohort population. European Prospective Investigation into Cancer and Nutrition. *Eur J Epidemiol* 2001;**17**:1047-53.

12.   Blokstra AS, Smit HA, Bueno-de-Mesquita HB, Seidell JC, Verschuren WMM.Monitoring van Risicofactoren en Gezondheid in Nederland (MORGEN-project), 1993–1997, Leefstijl-en risicofactoren: prevalenties en trends.*RIVM rapport*2005.

13.   Herings RM, Bakker A, Stricker BH, Nap G.Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts.*J Epidemiol Community Health* 1992;**46**:136-40.

14.   Rubin H.Multiple imputation for nonresponse in surveys.*Wiley series in probability and mathematical statistics. Applied probability and statistics.*John Wiley & Sons; 1987

15.   Cairns BJ, Liu B, Clennell S, Cooper R, Reeves GK, Beral V, Kuh D.Lifetime body size and reproductive factors: comparisons of data recorded prospectively with self reports in middle age.*BMC Med Res Methodol* 2011;**11**:7.

16.   Hall PS, Nah G, Howard BV, Lewis CE, Allison MA, Sarto GE, Waring ME, Jacobson LT, Manson JE, Klein L, Parikh NI.Reproductive Factors and Incidence of Heart Failure Hospitalization in the Women's Health Initiative*J Am Coll Cardiol* 2017;**69**:2517-2526.

17.   Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT.Resting heart rate and incident heart failure in apparently healthy men and women in the EPIC-Norfolk study.*Eur J Heart Fail* 2012;**14**:1163-70.

18.   Merry AH, Boer JM, Schouten LJ, Feskens EJ, Verschuren WM, Gorgels AP, van den Brandt

        PA.Validity of coronary heart diseases and heart failure based on hospital discharge and

        mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study.*Eur

        J Epidemiol* 2009;**24**:237-47.

19.   McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA.Validity of heart failure diagnoses in

        administrative databases: a systematic review and meta-analysis.*PLoS One* 2014;**9**:e104519.

20.   Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, Rand WM.Recall of

        early menstrual history and menarcheal body size: after 30 years, how well do women

        remember?*Am J Epidemiol* 2002;**155**: 672-9.

21.   Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, Ferreira T, He C, Chasman DI,

        Esko T, Thorleifsson G, Albrecht E, Ang WQ, Corre T, Cousminer DL, Feenstra B,

        Franceschini N, Ganna A, Johnson AD, Kjellqvist S, Lunetta KL, McMahon G, Nolte

        IM, Paternoster L, Porcu E, Smith AV, Stolk L, Teumer A, Tšernikova N, Tikkanen

        E, Ulivi S, Wagner EK, Amin N, Bierut LJ, Byrne EM, Hottenga JJ, Koller DL,

        Mangino M, Pers TH, Yerges-Armstrong LM, Zhao JH, Andrulis IL, Anton-Culver H,

        Atsma F, Bandinelli S, Beckmann MW, Benitez J, Blomqvist C, Bojesen SE, Bolla MK,

        Bonanni B, Brauch H, Brenner H, Buring JE, Chang-Claude J, Chanock S, Chen J,

        Chenevix-Trench G, Collée JM, Couch FJ, Couper D, Coveillo AD, Cox A, Czene K,

        D'adamo AP, Smith GD, De Vivo I, Demerath EW, Dennis J, Devilee P, Dieffenbach

        AK, Dunning AM, Eiriksdottir G, Eriksson JG, Fasching PA, Ferrucci L,

        Flesch-Janys D, Flyger H, Foroud T, Franke L, Garcia ME, García-Closas M, Geller

        F, de Geus EE, Giles GG, Gudbjartsson DF, Gudnason V, Guénel P, Guo S, Hall P,

        Hamann U, Haring R, Hartman CA, Heath AC, Hofman A, Hooning MJ, Hopper JL, Hu FB,

        Hunter DJ, Karasik D, Kiel DP, Knight JA, Kosma VM, Kutalik Z, Lai S, Lambrechts

        D, Lindblom A, Mägi R, Magnusson PK, Mannermaa A, Martin NG, Masson G, McArdle

        PF, McArdle WL, Melbye M, Michailidou K, Mihailov E, Milani L, Milne RL,

Nevanlinna H, Neven P, Nohr EA, Oldehinkel AJ, Oostra BA, Palotie A, Peacock M, Pedersen NL, Peterlongo P, Peto J, Pharoah PD, Postma DS, Pouta A, Pylkäs K, Radice P, Ring S, Rivadeneira F, Robino A, Rose LM, Rudolph A, Salomaa V, Sanna S, Schlessinger D, Schmidt MK, Southey MC, Sovio U, Stampfer MJ, Stöckl D, Storniolo AM, Timpson NJ, Tyrer J, Visser JA, Vollenweider P, Völzke H, Waeber G, Waldenberger M, Wallaschofski H, Wang Q, Willemsen G, Winqvist R, Wolffenbuttel BH, Wright MJ; Australian Ovarian Cancer Study; GENICA Network; kConFab; LifeLines Cohort Study; InterAct Consortium; Early Growth Genetics (EGG) Consortium, Boomsma DI, Econs MJ, Khaw KT, Loos RJ, McCarthy MI, Montgomery GW, Rice JP, Streeten EA, Thorsteinsdottir U, van Duijn CM, Alizadeh BZ, Bergmann S, Boerwinkle E, Boyd HA, Crisponi L, Gasparini P, Gieger C, Harris TB, Ingelsson E, Järvelin MR, Kraft P, Lawlor D, Metspalu A, Pennell CE, Ridker PM, Snieder H, Sørensen TI, Spector TD, Strachan DP, Uitterlinden AG, Wareham NJ, Widen E, Zygmunt M, Murray A, Easton DF, Stefansson K, Murabito JM, Ong KK.Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche.*Nature* 2014;**514**:92-97.

22.   Elks CE, Ong KK, Scott RA, van der Schouw YT, Brand JS, Wark PA, Amiano P, Balkau B, Barricarte A, Boeing H, Fonseca-Nunes A, Franks PW, Grioni S, Halkjaer J, Kaaks R, Key TJ, Khaw KT, Mattiello A, Nilsson PM, Overvad K, Palli D, Quirós JR, Rinaldi S, Rolandsson O, Romieu I, Sacerdote C, Sánchez MJ, Spijkerman AM, Tjonneland A, Tormo MJ, Tumino R, van der A DL, Forouhi NG, Sharp SJ, Langenberg C, Riboli E, Wareham NJ.Age at menarche and type 2 diabetes risk: the EPIC-InterAct study.*Diabetes Care* 2013;**36**: 3526-34.

23.   Charalampopoulos D, McLoughlin A, Elks CE, Ong KK.Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. *Am J Epidemiol* 2014;**180**: 29-40.

24.   Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry *J Am Coll Cardiol* 2007;**50**: 768-77.

25.   Chinali M, Joffe SW, Aurigemma GP, Makam R, Meyer TE, Goldberg RJ. Risk factors and comorbidities in a community-wide sample of patients hospitalized with acute systolic or diastolic heart failure: the Worcester Heart Failure Study. *Coron Artery Dis* 2010;**21**: 137-43.

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

	Age at menarche						
Variables	**8-11**	**12**	**13**	**14**	**15**	**16-20**	**Overall cohort**
	N=3,212	N=5,883	N=7,012	N=6,044	N=3,270	N=2,560	N=28,508
Age at recruitment, median (IQR), years	51.5 (42.8-57.2)	52.3 (44.5-58.3)	52.0 (44.0-58.3)	53.1 (47.8-59.2)	54.5 (49.6-61.3)	56.8 (50.4-63.4)	52.9 (46.9-59.1)
Highest education[a],n missing	9	17	23	10	12	14	202
Low education level n (%)	1,358 (42.4%)	2,304 (39.3%)	2,567 (36.7%)	2,641 (43.8%)	1,499 (46.0%)	1,338 (52.6%)	11,929 (41.8%)
Middle education level n (%)	1,333 (41.6%)	2,492 (42.5%)	2,987 (42.7%)	2,256 (37.4%)	1,213 (37.2%)	882 (34.6%)	11,304 (39.7%)
High education level n (%)	512 (16.0%)	1,070 (18.2%)	1,435 (20.5%)	1,137 (18.8%)	546 (16.8%)	326 (12.8%)	5,073 (17.8%)
Body mass index, mean (SD), kg/m^2	26.7 (4.7)	25.9 (4.2)	25.5 (4.0)	25.3 (4.0)	25.3 (4.0)	25.4 (4.2)	25.7 (4.2)
HDL-cholesterol, mean (SD), mmol/l	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)
Non-HDL-cholesterol, mean (SD), mmol/l	4.1 (1.1)	4.0 (1.1)	4.0 (1.1)	4.1 (1.1)	4.1 (1.1)	4.2 (1.1)	4.1 (1.1)
Hypertension, Yes n (%)	1,369 (42.6%)	2,385 (40.5%)	2,652 (37.8%)	2,329 (38.5%)	1,261 (38.6%)	1,054 (41.2%)	11,271 (39.5%)
CHD prior to HF, Yes n (%)	51 (1.6%)	92 (1.9%)	90 (1.3%)	83 (1.4%)	54 (1.7%)	62 (2.4%)	461 (1.6%)
T2D prior to HF, Yes n (%)	64 (2.0%)	113 (1.9%)	83 (1.2%)	100 (1.7%)	49 (1.5%)	59 (2.3%)	517 (1.6%)
Smoking status, n missing	3	5	5	6	1	0	136
Yes n (%)	1,048 (32.7%)	1,719 (29.2%)	1,891 (27.0%)	1,592 (26.4%)	834 (25.5%)	691 (27.0%)	7,871 (27.6%)
In the past n (%)	976 (30.4%)	1,788 (30.4%)	2,257 (32.2%)	1,951 (32.3%)	1,066 (32.6%)	767 (30.0%)	8,942 (31.4%)
No n (%)	1,185 (36.9%)	2,371 (40.3%)	2,859 (40.8%)	2,495 (41.3%)	1,369 (41.9%)	1,102 (43.0%)	11,559 (40.5%)
Pack years smoking[b], median (IQR)	13.5 (5.0-24.0)	12.0 (4.2-21.9)	10.5 (3.8-21.0)	11.0 (3.9-21.8)	12.3 (4.3-23.3)	13.1 (4.8-23.8)	11.7 (4.1-22.2)
Alcohol use, n missing	101	220	265	269	140	107	1209
No never n (%)	283 (9.1%)	440 (7.8%)	532 (7.9%)	440 (7.6%)	235 (7.5%)	185 (7.5%)	2,130 (7.8%)
No, I quit n (%)	23 (0.7%)	35 (0.6%)	60 (0.9%)	35 (0.6%)	16 (0.5%)	18 (0.7%)	187 (0.7%)

	Age at menarche						
< 1 Drink/week n (%)	1,146 (36.8%)	1,918 (33.9%)	2218 (32.9%)	1,991 (34.5%)	1,067 (34.1%)	970 (39.5%)	9,498 (34.8%)
Yes n (%)	1,659 (53.3%)	3,270 (57.7%)	3,938 (58.4%)	3,309 (57.3%)	1,812 (57.9%)	1,280 (52.2%)	15,481 (56.7%)
Age at menarche, median (IQR) years	11.0 (11.0-11.0)	12.0 (12.0-12.0)	13.0 (13.0-13.0)	14.0 (14.0-14.0)	15.0 (15.0-15.0)	16.0 (16.0-16.0)	13.0 (12.0-14.0)
Menopausal status,							
Premenopausal n (%)	1,155 (36.0%)	1,947 (33.1%)	2,447 (34.9%)	1,859 (30.8%)	872 (26.7%)	551 (21.5%)	8,886 (31.2%)
Perimenopausal n (%)	647 (20.1%)	1,072 (18.2%)	1,291 (18.4%)	1,084 (17.9%)	537 (16.4%)	390 (15.2%)	5,140 (18.0%)
Naturally postmenopausal n (%)	1,278 (39.8%)	2,664 (45.3%)	3,070 (43.8%)	2,903 (48.0%)	1,741 (53.2%)	1,491 (58.2%)	1,3472 (47.3%)
Bilateral oophorectomy n (%)	132 (4.1%)	200 (3.4%)	204 (2.9%)	198 (3.3%)	120 (3.7%)	128 (5.0%)	1,010 (3.5%)

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 2 Hazard ratio's per year increasing age at menarche for risk of heart failure (HF)

	HR per year AAM (95%CI)	p-value
Model 1	0.95 (0.90-1.00)	0.056
Model 2	0.95 (0.90-1.00)	0.038
Model 3	0.95 (0.91-1.00)	0.042
Mediations		
Model 3 plus BMI	0.96 (0.91-1.01)	0.130
Model 3 plus prior CHD	0.96 (0.91-1.00)	0.095
Model 3 plus hypertension	0.96 (0.91-1.01)	0.100
Model 3 plus prevalent T2D	0.97 (0.92-1.00)	0.274

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).