

Is It All Determined at Menarche?

Renate B. Schnabel, MD, MSc

Sex differences in cardiovascular disease (CVD) risk are well established and have entered risk prediction tools and recommendations for sex-specific interventions.¹ Menstrual and reproductive factors may help us understand the female advantage in common cardiovascular lifetime diseases with an obvious protection during the reproductive period. Important developmental and hormonal transitions during a woman's life are menarche and menopause. Menarche occurs late in pubertal development as an indicator of the beginning of the reproductive period.

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Whereas menopause has been the focus of an abundance of investigations over decades, menarche has received increasing attention only over the last years. From recent publications and first meta-analyses, it appears that age at menstrual onset is related to cardiovascular risk factors in later life and CVD outcomes across ethnicities.^{2,3} Pubertal changes leading to menarche are determined by a fine-tuned interplay of endogenous hormonal regulations and complex modifying factors. In particular, nutritional status and childhood adiposity with the consecutive hormonal and metabolic changes have been shown to be related to accelerated pubertal timing and menstrual onset.^{4,5} Early menarche predicts higher body mass index (BMI) and adiposity in adult life.^{3,4} Furthermore, early menarche has been associated with hypertension, metabolic syndrome, impaired glucose tolerance, and type 2 diabetes mellitus, which mediate CVD.³ Thus, a direct or indirect association with CVD in later life must be assumed. However, former studies and meta-analyses across ethnicities have remained inconsistent in terms of the associations between menarche timing and CVD outcomes.^{2,3} The studies were characterized by heterogeneity between cohorts and differences in adjustment for confounders and end-point definitions.

In this context, the article by Canoy and colleagues⁶ in this issue of *Circulation* provides robust novel data on >1 million middle-aged UK women invited for routine breast cancer screening. They were followed up for coronary heart disease, stroke, hypertension, and coronary heart disease mortality for

an average of 11.6 years. Outcomes were available from linkage with national and hospital databases with almost complete follow-up.

Sufficient numbers allowed the calculation of solid estimates in the early and late periods of menstrual onset for single years of age. Usually, menstrual onset before 12 years of age is defined as early menarche. Canoy and colleagues were able to examine the risk of menstrual onset at ≤ 10 and 11 years of age with good power. They showed that the younger age groups were associated with a higher relative risk of coronary heart disease than the 13-year-old group. Similarly, for the age groups of ≥ 14 years, a rather exponential increase in coronary heart disease risk became apparent. Stroke and incident hypertension showed highest relative risks for very early and late menarche.

Previous data suggested a U-shaped association for all-cause mortality and coronary heart disease deaths.⁷⁻⁹ The present study now demonstrates a similar pattern for 2 major CVDs and their risk factor, hypertension. Such findings appear biologically plausible. As often seen in nature, extremes are detrimental.

Findings were consistent across categories of possible modifiers and confounders, that is, BMI, smoking, or socioeconomic status. Recent reports suggested an association between timing of menarche and CVD in nonsmoking women or a study population in which the prevalence of smoking was low.^{2,10} The present study, however, could not support these results. It needs to be considered that associations with smoking habits underlie considerable confounding, which may account for discrepant findings.

Similar to earlier studies,⁹ the article by Canoy et al showed a significant association between coronary heart disease mortality and early menarche, but statistical significance was not reached for late menarche. A comparatively small number of events limited these analyses.

Furthermore, the study examined women in their 50s between 1996 and 2001. Ongoing trends in younger age of menarche onset have been observed,¹¹ which could mean shifts in the results in more contemporary populations. However, expected differences probably would be minor and might even be more pronounced with an increasing proportion of individuals with earlier age at menstrual onset.

The exposure age at menarche was recorded by questionnaire in middle age and may have led to recall error. However, no significant differences were demonstrated in a subgroup of a sample made up of a birth cohort in which age at menarche was registered 2 times, at puberty and in middle age. Most likely, misclassification would have been nondifferential.

Observations presented in the article certainly need validation in independent cohorts and across ethnicities. These efforts will be facilitated by the existence of large-scale consortia that have been formed to investigate the pathophysiology

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From the University Heart Center, Department of General and Interventional Cardiology, Hamburg, Germany; and DZHK (Deutsches Zentrum fuer Herz-Kreislauf-Forschung e.V.), partner site Hamburg/Kiel/Luebeck, Germany.

Correspondence to Renate B. Schnabel, MD, MSc, Department of General and Interventional Cardiology, University Heart Center Hamburg-Eppendorf, Building East 70 (O70), Martinistrasse 52, 20246 Hamburg, Germany. E-mail r.schnabel@uke.de

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and genetics of pubertal timing and menarche. Overall, Canoy and colleagues performed one of the largest studies on menarche and CVD risk. They provide substantial evidence of the importance of menarcheal timing and CVD outcomes in later life at the population level.

In light of the findings of Canoy and colleagues, the next obvious steps are to better characterize the determinants of menarche. As outlined, menarche is the result of the sum of diverse factors. It will be a challenge to dissect the components of pubertal timing and their relation to CVD risk owing to the substantial overlap of risk factors and the unclear direction of potential causality. For example, it has been shown that childhood overweight and adiposity are related to earlier menarche and that earlier menarche is associated with higher BMI in later life.^{3,12} Childhood BMI correlates highly with adult BMI.¹³ Therefore, the relationship between menarche and CVD risk may be confounded by childhood BMI. Although no measures of childhood obesity were available, the data by Canoy and colleagues and previous publications^{2,3} indicate that associations of menarche with CVD risk are not fully explained by BMI.

Efforts to describe the mechanisms of menarche and their role in the causal pathway of CVD will be supported by the workup of novel genetic findings and pathway analyses. About half of the variance in age at menstrual onset is explained by genetic variation.¹⁴ Recent genome-wide association studies have underscored the multifactorial regulation of menarche, including distinct pathophysiological pathways.¹⁵ More than 100 genomic loci with minor effect sizes have been identified for age at menarche. The overlap with common polymorphisms related to energy homeostasis and adult BMI is striking. It suggests a shared genetic etiology that needs further examination in relation to CVD risk.

In the meantime, several clinical implications can be derived: We need to learn that female-specific risk indicators may be a valuable source for refining a woman's individual CVD risk assessment. For a general cardiologist, a seemingly distant event such as puberty and age at menarche may provide valuable information. Besides pregnancy-associated complications and menopausal characteristics, pubertal development and menarche may become a routine part of a female's medical history not only for the general practitioner but also for the cardiologist. Menstrual onset is a critical event in a woman's maturation and is recalled fairly accurately. Thus, it constitutes an easily assessed marker for pubertal processes and timing.

Early CVD risk assessment around menarche, with the major part of the lifespan still to come, offers opportunities. In many countries, interactions with the medical system are frequent around menarche and may offer CVD risk evaluation, counseling, and early interventions long before the cardiologist enters the stage. Gynecologists and general practitioners will need to take over this responsibility. Closer cooperation and uniform recommendations among disciplines need to be established.

At present, we are only at the beginning of understanding the complex associations of puberty, reproductive factors, and CVD risk, and we still far from defining effective screening programs and interventions. The long story of hormone

replacement therapy for CVD prevention has proven that a simple concept may not be generally effective. With the interactions of genetics, adiposity, hypertension, socioeconomic status, and family environment, among others, as triggers of menarche, lifestyle changes and a multilevel intervention are the most likely targets for preventive efforts.

CVD risk certainly is not fully explained and determined at the time of menarche. However, knowing puberty-associated risk indicators may help to identify individuals at increased risk of CVD and to tailor diagnostic and preventive strategies over a lifetime. Successful efforts would have profound public health implications, eventually affecting half of our population.

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