

Promoting Healthy Longevity Should Start Young: A Life Course Journey

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Introduction

Throughout a woman's life, several unique health characteristics are related to an increased risk of later disease morbidity and/or premature mortality (Fig. 1). For instance, these include early age at menarche^{1,2} (ie, "short, irregular or long menstrual cycles")^{3,4}, a history of infertility⁵, pregnancy loss⁶, several major pregnancy complications (eg, preeclampsia, gestational hypertension, gestational diabetes mellitus (GDM) and preterm delivery)^{7–9}, and menopause characteristics (eg, long menopause transition period, early age at menopause, and the presence of vasomotor symptoms).^{10,11} Additionally, accumulating evidence supports the intergenerational impacts of maternal health and well-being on child health.¹² Taken together, these associations imply that achieving healthy longevity is a lifelong journey. The promotion of healthy longevity should start at a young age and not deferred until later in life, to enhance the health and life quality of both women and their offspring. In this perspective article, we aim to discuss the relevance of reproductive health and pregnancy outcomes for promoting healthy longevity for young, middle-aged, and future elderly women, as well as the next generations, based on results from large human epidemiological studies.

Menstrual health and morbidities/premature mortality

Menstrual health characteristics, such as the regularity and length of menstrual cycles, have been regarded as an indicator of the overall health of reproductive-age women. For instance, both irregular and long menstrual cycles have been related to

increased rates of cardiovascular diseases³ and premature mortality.¹³ Notably, women who had irregular, frequent, or infrequent menstrual cycles were at a higher risk of several cardiometabolic diseases, including type 2 diabetes, compared to women with a regular menstrual cycle or a normal cycle frequency, as indicated by a retrospective matched cohort study involving over 700,000 women from the United Kingdom.³ Moreover, women with usually irregular or always irregular menstrual cycles were found to have a greater risk of premature mortality starting from 50 years old.¹³ All these associations were observed after the adjustment for major confounders, such as women's body adiposity status. These findings suggest that menstrual cycle characteristics might serve as a proxy for the overall health status of reproductive-age women and may help identify high-risk women in early and middle-aged adulthood.

Pregnancy complications and premature mortality

Pregnancy is a critical event in parous women's lives that could have substantial lifelong health implications. Throughout pregnancy, women's body experiences tremendous cardiometabolic and hormonal changes. These changes may be considered as stress tests or challenges to identify women who are at greater risk of developing cardiometabolic diseases later in their lives.¹⁴ Accumulating data from large epidemiological studies have demonstrated that pregnancy complications may help identify women at a higher risk for chronic diseases in later life. For example, women who experienced GDM were related to more than a seven-fold increased risk of developing type 2 diabetes later in life, even though their blood glucose levels often return to normal after delivery.¹⁵ Women with a history of GDM were also found to exhibit a higher risk for cardiovascular diseases, as well as renal and liver dysfunctions.^{16–18} Similarly, women who experienced other common pregnancy complications such as preterm delivery or hypertensive disorders during pregnancy, were related to an increased risk for cardiovascular diseases in later life.¹⁹ For instance, we recently found that women who experienced preeclampsia, gestational hypertension, GDM, or preterm delivery have an increased risk of premature mortality in the next 50 years after the index pregnancy, based on the data from a US diverse cohort, which enrolled 45,000 Caucasian and African American pregnant women between the 1950s and 1960s.⁷ Within the same cohort, we also observed that women with gestational weight gain above the recommendations had a higher incidence of mortality from heart disease or diabetes than women who followed the recommendations.²⁰ These findings support the importance of achieving healthy gestational weight gain within recommendations, emphasizing

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Unique health characteristics for women

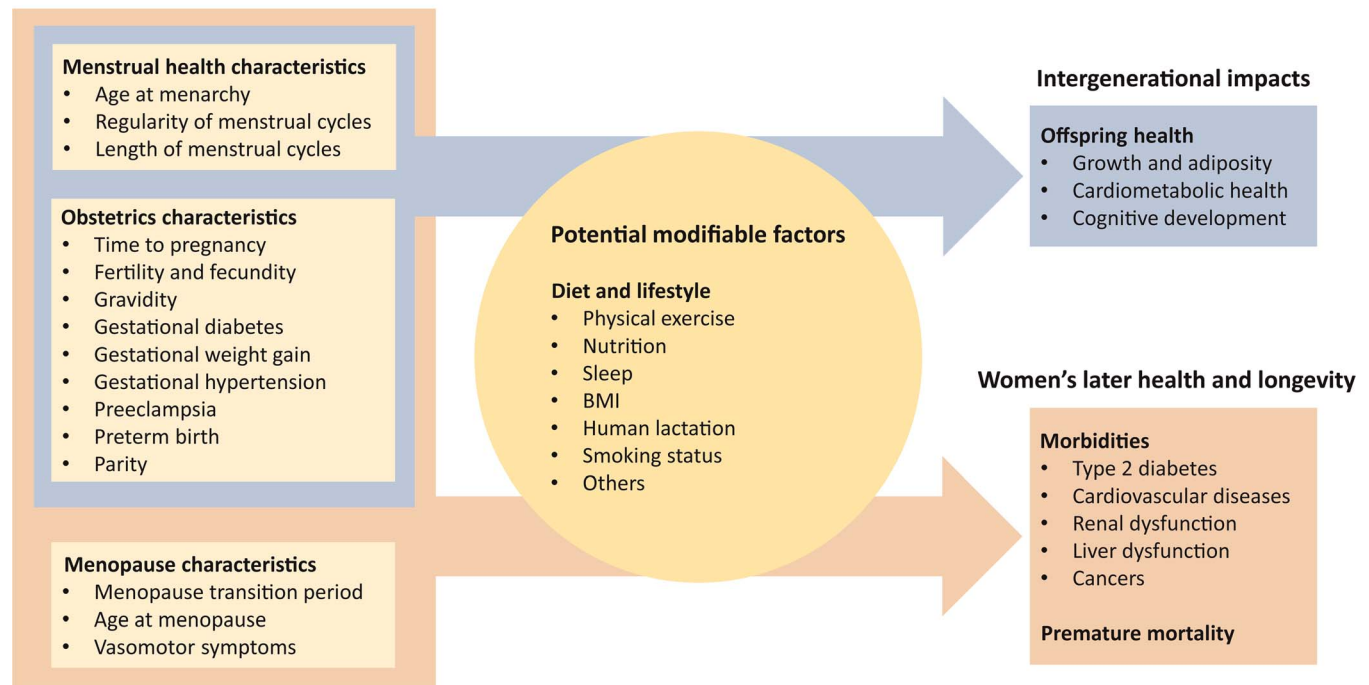


Figure 1. Reproductive and obstetric health status of women and its association with long-term morbidities and mortality. BMI: Body Mass Index.

that the implications may extend beyond the pregnancy period to long-term health, including cardiovascular mortality.

Intergenerational impacts of women's health and links to premature mortality

The health status of reproductive-age women is important not only for their own later health but also for the health of their offspring. The first 1,000 days of life (from conception to the 2 years of the child) has been regarded as a critical period for short- and long-term health.¹² Using gestational diabetes as an example, the “diabetes begetting diabetes vicious circle” is well-known. Offspring born from pregnancies complicated by GDM are at high risk for developing cardiometabolic disorders, such as obesity and impaired glucose tolerance. When these individuals become pregnant, they are more likely to develop GDM themselves, thereby creating a vicious circle that may impact multiple generations.²¹ Birth weight, a proxy of in-uterine growth measurement, has been repeatedly related to morbidities, such as type 2 diabetes and cardiovascular diseases in multiple studies and recently with premature mortality.

In summary, emerging and accumulating evidence supports links between major women's reproductive health events with later disease risk and premature mortality. These results can help to identify women at high risk for targeted intervention for improving healthy longevity.

Healthy diet and lifestyle promotion are promising for improving women's health and longevity

Identifying these high-risk populations is the first step to promoting healthy longevity. The next critical step is to highlight factors that could be helpful to improve the health

and longevity among these high-risk women, as such to lower morbidities and premature mortality.

In that context, several studies have shown that a healthy diet and adequate lifestyle can lower the risk of adverse reproductive and pregnancy complications, as well as the risks of chronic diseases among high-risk women, and therefore increase their life expectancy. For instance, a previous study highlighted that three commonly recommended healthy dietary patterns (ie, Mediterranean diet, Healthy Eating Index based on current US dietary guidance, and the DASH diet (Dietary Approaches to Stop Hypertension)) in early pregnancy and midpregnancy were related to reduced risks of major pregnancy complications, such as preterm delivery, preeclampsia, gestational hypertension, and GDM.²² We also previously found that 46% of GDM cases may be prevented by adopting four factors: healthy diet, regular exercise, normal BMI, and not smoking.²³ In another study, based on more than 4,000 GDM cases followed up for more than 30 years, we observed that adopting a healthy diet and lifestyle is related to a 92% lower risk for T2D among women with a history of GDM.²⁴ Moreover, a recent meta-analysis concluded that changing a Western diet to an optimal diet could increase life expectancy by more than 10 years.²⁵ Authors concluded that the largest gains would be made by eating more legumes, whole grains, and nuts, and less red meat. They also emphasized that the earlier the dietary changes are initiated in life, the larger the gain in life expectancy.

Discussion

In this perspective article, we have discussed compelling evidence supporting the notion that promoting longevity should start young, with keen attention to women's health during their reproductive years. All the studies presented are based on

large human populations. In contrast to animal studies or randomized controlled trials, population studies cannot establish causality. Nevertheless, the presented evidence from high-quality human population data, at least, highlights the significance of reproductive health events occurring early or in midlife for women across their lifespan and generations.

Future direction

Future research should pursue the assessment of risk factors and biomarkers to enable the early identification of high-risk women and then to follow up these women, intervene, and prevent complications. Diet and lifestyle modifications have been demonstrated effective in research studies; however, achieving sustainable behavior modifications remains challenging. Future endeavors for developing and implementing sustainable healthy diets and lifestyle modifications at a population level shall involve multidisciplinary efforts and the participation of political decision-makers. In addition, it should be pointed out that studies on long-term health implications of reproductive and obstetric complications among the Asian population are emerging but still very limited.^{26,27} Indeed, even though Asians represent more than 60% of the world's population, only 10% of clinical trials and genetic databases have Asian representation. This underrepresentation could lead to important disparities in health outcomes for the Asian population and should, therefore, be addressed in future studies.

Conclusion

To conclude, the results of large human epidemiological studies emphasize the long-term impacts of women's reproductive health events on their later health and the health of their offspring, highlighting the importance of considering these early characteristics to promote healthy longevity. Future research should pursue the assessment of factors and biomarkers to identify women at high risk early in life and to support their behavior change, notably among the Asian population.

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Author Contributions

Cuilin Zhang conceptualized, contributed to the discussion, drafted and edited the manuscript, and supervised the paper. Claire Guivarch drafted the manuscript and contributed to the discussion. Both authors reviewed and approved the final version of the paper, and contributed to the design and the content of the figure.

Conflicts of Interest

None.

Editor Note

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