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Secular trends in premature and early menopause in low-income and middle-income countries

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ABSTRACT

Background While secular trends in high-income countries show an increase in the mean age at menopause, it is unclear if there is a similar pattern in low-income and middle-income countries (LMICs), where women's exposure to biological, environmental and lifestyle determinants of menopause may differ. Premature (before age 40 years) and early (ages 40–44 years) menopause could have negative repercussions on later life health outcomes which in ageing societies could mean further stress on low-resource health systems. An evaluation of such trends in LMICs has been hampered by the suitability, quality and comparability of data from these countries.

Methods Using 302 standardised household surveys from 1986 to 2019, we estimate trends and CIs using bootstrapping in the prevalence of premature and early menopause in 76 LMICs. We also developed a summary measure of age at menopause for women who experience menopause before the age of 50 years based on demographic estimation methods that can be used to measure menopausal status in surveys with truncated data.

Results Trends indicate an increasing prevalence of early and premature menopause in LMICs, in particular in sub-Saharan Africa and South/Southeast Asia. These regions also see a suggested decline of the mean age at menopause with greater variation across continents.

Conclusions This study enables the analysis of menopause timing by exploiting data generally used for the study of fertility by methodologically allowing the use of truncated data. Findings show a clear increase in prevalence of premature and early menopause in the regions with the highest fertility with possible consequences for later life health. They also show a different trend compared with high-income regions, confirming a lack of generalisability and the importance of accounting for nutritional and health transitions at the local level. This study calls for further data and research on menopause on a global scale.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Timing of menopause is generally influenced by genetic, biological, environmental and socio-economic factors.
⇒ So far, most of the evidence on secular trends in menopause (including early and premature) relates to high-income countries.
⇒ Premature (before age 40 years) and early (40–44 years) menopause are linked to a higher risk of mortality and neurological diseases among others.
⇒ In settings with higher fertility and higher burden of adverse reproductive outcomes, there is a need to understand levels and trends.

WHAT THIS STUDY ADDS

⇒ The study of menopause in low-income and middle-income countries (LMICs) is very timely due to the increasing demands women face on their mid-life and rapid ageing occurring.
⇒ This paper is the first to assess secular levels and trends of premature and early menopause across a wide range of LMICs.
⇒ In addition, it is the first to use the whole of the Demographic and Health Surveys (n=302) to estimate levels of potential timing of menopause using a demographic tool useful for data which are truncated at the age of 49 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Beyond the data and methodological novelty which will make a breakthrough for future analyses of menopause in low-resource countries, this study is particularly important as the potential negative impact of early menopause on women's physical and mental health could be potentially more significant in low-resource countries.
⇒ By highlighting the increase of prevalence in early menopause in low-resource settings, we call for further research on the potential impact this could have later in life and eventually on health systems in low-resource countries.
⇒ The ramifications of the results cut across public health, health policy, social epidemiology and demography as well as primary healthcare studies.

INTRODUCTION

Menopause is defined as the cessation of ovarian function leading to oestrogen deficiency and is typically measured as the absence of menstruation for 12 consecutive months.[1] Menopause usually occurs between the ages of 45 and 55 years and, with changes in nutrition and health experiences across the life-course which have led to an increase in life expectancies, it is increasingly now

a mid-life stage. Understanding the timing and mechanisms of the age of menopause is important, as both early and late menopause have potential impacts on several health outcomes.[2–4]

The aim of this paper is to assess trends in the prevalence of premature and early menopause, as well as trends in mean age at menopause, for women aged 49 years and below in low-income and middle-income countries (LMICs) and to look at patterns across time, regions and countries.[5] Using standardised, cross-country underused measures with techniques derived from demographic methods, we also calculate the truncated singulate mean age at menopause (SMAM)[6] before the age of 50 years across 302 datasets. Because the datasets we use preclude measuring absolute mean age at menopause as they do not interview women after age 49 years, we look at trends in the SMAM which allows for analysis of truncated data across time and place.

Historically, since the sixth century AD, age at menopause has been consistently reported at around 50 or 51 years, or generally end of 40s beginning of 50s, with the suggestion that there are few factors that influence its timing.[7] More recent estimates, largely from high-income countries (HICs), extend the range of average age at menopause from 47 to 53 years.[8 9] Premature (before the age of 40 years) and early (between 40 and 44 years, i.e. before age 45) menopause are usually estimated to occur in approximately 1%–9% and 5%–9% of women, respectively,[10] again with estimates mostly derived from samples from HICs. However, in-depth studies have shown that both early and premature menopause patterns vary greatly by factors such as ethnicity, place of birth and education level,[11–13] potentially pointing to a role for socio-economic, environmental and cultural influences in the timing of menopause. These context-dependent factors can make generalisations across time and place—including from HICs to LMICs—challenging.

Research from Europe and the USA shows secular trends of delayed age at menopause.[14 15] Improved nutrition, changing lifestyles (eg, smoking), genetics and parity are all factors associated with changes in the timing of menopause.[14] While several studies have explored the secular trend in menopausal age, these are limited to HICs[16 17] and often only related to white women despite the evidence of clear differentials across ethnic groups where data are available. So far, there has been no study that systematically evaluates secular trends in menopause, as well as trends in premature and early menopause, in LMICs. Reasons for this gap are multifactorial but can be tied to a historical emphasis on prevention of unintended pregnancies in higher fertility settings, with little regard to postreproductive health of women.[18] Additionally, menopause is a challenging outcome to measure in surveys, as it does not occur as one single event (eg, unlike menarche), and menstruation can come and go for a period of up to 10 years.

For the few studies reporting timings of menopause in LMICs, the evidence is split. On one hand, scant evidence for LMICs suggests a younger average age of onset compared with HICs,[19] with likely cross-regional variation ranging from the late 40s in LMICs to early 50s in HICs.[20] Reports of earlier age at menopause in LMICs are common both in studies conducted in small-scale societies and among less isolated populations,[21] for example, in the Agta Negrito in the Philippines (mean=44 years[22]) and in India and Pakistan (range=44–48 years, median=47 years[23–25]). On the other hand, there is also evidence of countries reporting estimated average ages well within HICs levels, such as a study of seven Southeast Asian countries (not all LMICs) that estimated a median age at menopause at 51.09 years.[26] Another study looking at international variability in timing of reproductive events[27] found median ages at menopause at 49–52 years. Reports of later ages at menopause compared with HICs are unusual, although one study reported a mean age of 53.16 years in Turkey.[28] Differentials in trends also show a mixed picture. A study in Latin America showed that women with lower incomes and lower education levels generally reported an earlier onset of menopause.[29] Whereas, a more recent study in Indonesia using Demographic and Health Surveys (DHS) data showed a higher prevalence of early and premature menopause among higher educated and urban women.[30]

Premature and early menopause are commonly associated with higher levels of smoking, obesity, childlessness and malnutrition.[10] As some of these factors have been increasing in recent decades, it is unclear whether these secular changes relate to a delayed age at menopause and levels of premature and early menopause. This is particularly important in LMICs where the epidemiological and nutritional transitions have been occurring at different paces. However, causes of premature and early menopause remain elusive and inconsistent across studies. While there is evidence in some studies of early menarche being linked to early menopause, this is not replicated in other settings.[15 31] Early life circumstances, genetics, ethnicity and socio-economic status have all been linked with menopause timing.[10] Nutrition above all has been at the centre of changes, with a strong influence of the transitions to healthier diet first (delayed menopause) and then diets in saturated fats (early menopause). Environmental studies also show that exposure to endocrine disruptors in the form of air and water pollution is also increasing, with a negative impact on ovarian function, which could accelerate the timing of natural menopause.[32] Fertility has been found to have mixed results with European studies showing higher fertility leading to delayed age at menopause and no effect in other regions.[10] Even in HICs where we have seen a delay in the mean age at menopause, the association with the prevalence of early and premature menopause is still not clear. Overall, the evidence shows us that inferences cannot be made about trends. Given the overall lack of evidence on the impact of premature and early menopause mainly in low-income settings, there is a need to provide clearer evidence on patterns and trends.

Table 1 Mean menopause values and bootstrapped CIs by world region (DHS 1985–2019)

	Premature (%)			Early (%)			SMAM (years)		
	Mean	SE	95% CI	Mean	SE	95% CI	Mean	SE	95% CI
Central Asia	1.2	0.1	1.0 to 1.4	1.6	0.1	1.49 to 1.76	45.3	0.3	44.8 to 45.8
Latin America and Caribbean	1.5	0.3	1.0 to 2.0	1.9	0.3	1.3 to 2.4	44.4	0.1	44.2 to 44.6
North Africa/West Asia/Europe	0.1	0.2	−0.4 to 0.5	1.4	0.7	−0.6 to 3.4	44.7	0.3	44.1 to 45.3
South and Southeast Asia	2.7	0.4	1.8 to 3.5	4.5	0.8	2.9 to 6.1	43.7	0.1	43.0 to 44.0
Sub-Saharan Africa	0.9	0.2	0.6 to 1.3	2.4	0.3	1.7 to 3.0	44.1	0.1	44.0 to 44.3

95% CI, 95% Confidence Interval; DHS, Demographic and Health Surveys; SE, Standard Error; SMAM, Singulate Mean Age at Menopause.

Studying premature and early menopause is important as they are linked to an increase in cardiovascular diseases and hypertension.[33] They may also confer an increased risk of overall mortality, neurological diseases, psychiatric diseases and osteoporosis among others.[5] In LMICs, compared with HICs, women reaching mid-life can expect to have started childbearing earlier, to have a higher fertility, a higher number of pregnancies that have resulted in either miscarriage, abortion or stillbirths (and more pregnancies resulting in infant deaths) and less access to healthcare.[18] These reproductive features could also have implications for the timing of menopause and later life health.[8] In already stretched health and social care systems, the impact of an increasing ageing population of women with further health issues could prove challenging. Mapping the timing of menopause in LMICs is particularly crucial at this stage as, due to a growing ageing population and longer life expectancies, women in these regions will spend a significant portion of their lives in postmenopause.[34]

METHODS

We analysed data from all available (n=302) standard household surveys from the DHS programme from the years 1985 to 2019, with 76 LMICs represented. The DHS are nationally representative household surveys that collect standardised information on key population and health indicators. Historically, DHS have provided a wealth of data on women's reproductive health in LMICs but have seldom been used to monitor trends in menopausal status despite the inclusion of a question on the time since last menstrual period being asked since the first round in the 1980s. Although DHS data are limited to women aged 15–49 years (hence often premenopausal), there is a need to think more creatively about the way we can explore and meaningfully use this standardised multicountry data that have been collected over several decades.

Since the first round of surveys in the 1980s, women aged 15–49 years have been asked the following question: "When did your last menstrual period start?". Ten of the surveys included in our study also included a separate measure of hysterectomy, but to ensure standardisation across surveys, we did not run a separate analysis without women who had a hysterectomy. We excluded datasets which were special data collection efforts and for which the sampling frame and the questionnaire deviated from the standard one. While retrospective recall bias from the respondent on her last menstruation is possible, the manner in which the question was asked and the distributions across time and countries show the data to be of good quality. Furthermore, a strength of these data is that they rely on reporting of date of last menstrual period rather than on perceptions of menopause.

The DHS programme identifies a woman as menopausal if they are not pregnant, not postpartum amenorrhoeic and have not had a period in the *6 months* preceding the survey; women are also considered to be menopausal if they self-report they are in menopause or had a hysterectomy on the question related to current contraceptive use (https://dhsprogram.com/data/Guide-to-DHS-Statistics/Menopause.htm). We used a modification of this definition by extending the 6-month period to 12 months to align with clinical and epidemiological definitions of menopause and to avoid misclassifying women who are not menopausal yet. Twelve months is also the most commonly used definition in other surveys[35]. (An informal conversation with DHS staff highlighted how the 12 months was not settled until the mid-1990s and given the DHS had started collecting data since the 1980s to insure comparability they chose not to modify the definition.). We have therefore manually coded all 302 surveys calculating the age at menopause based on the age of the respondent at the interview and the time of the last reported menstrual period. We compared the distribution of women using the 6-month DHS definition vs the 12-month DHS definition and we found no major inconsistencies.

After menopausal women were identified, we estimated the prevalence of premature and early menopause, which captures the left tail of the menopause age distribution. We defined premature menopause as the percentage of women who were menopausal among those aged 30–39 years and early menopause as the percentage of women who were menopausal among those aged 40–44 years. For these calculations, all women in each age group, regardless of parity, sexual activity or contraceptive use status, were included in

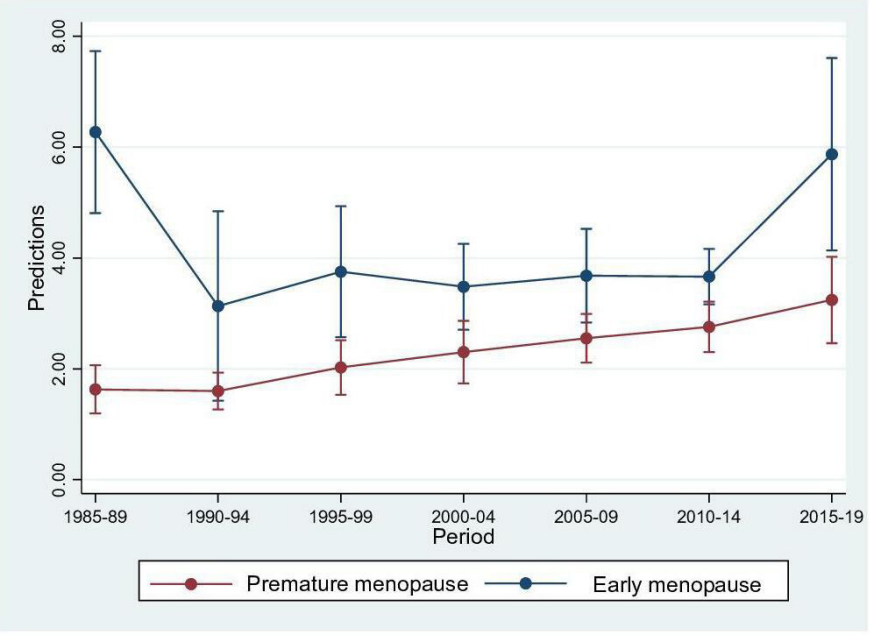

Figure 1 Global trends in early and premature menopause prevalence by survey period (DHS 1985–2019), with bootstrapped CIs. DHS, Demographic and Health Surveys.

the denominator. Including women who are still using contraception, in particular hormonal long acting which could potentially stop menstruation, could overestimate the number of menopausal women, as contraceptive use has been increasing over this time period throughout all the countries considered. However, this would affect both numerator and denominator. For this reason, we ran a robustness check keeping women using contraception in the sample for comparative purposes and also ran a separate sensitivity analysis for a subsample of countries where we excluded individuals using contraception. The results showed no significant difference in estimated trends. In addition, when we examined the correlation of contraceptive prevalence rates and prevalence of early and premature menopause, we found no to low positive correlations.

In addition to calculating the prevalence of early and premature menopause, we developed a novel summary measure of age at menopause based on the ages of women in the survey (aged 15–49 years). DHS only interviews women aged 15–49 years and will therefore not capture those whose menopause begins after this age.

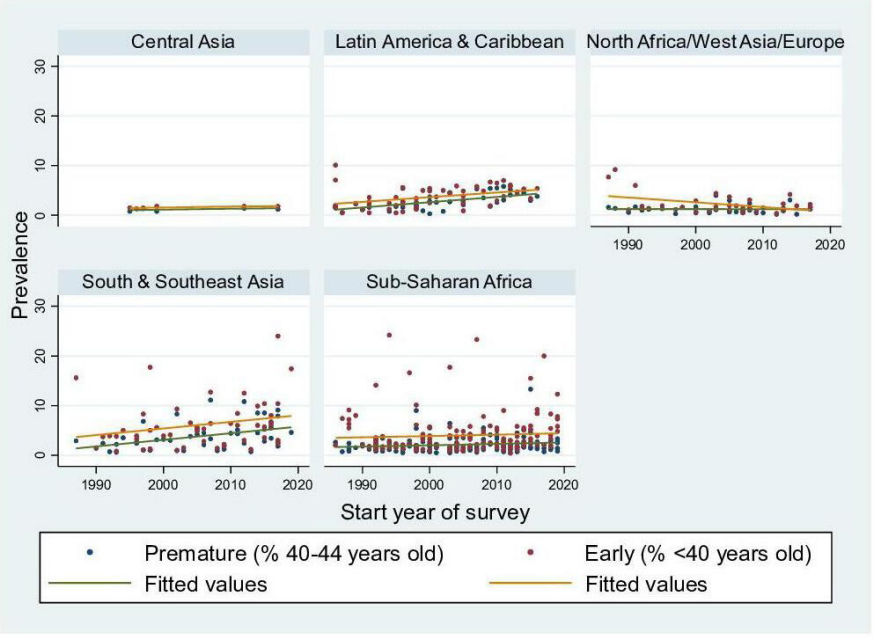

Figure 2 Regional trends in prevalence of premature and early menopause (DHS 1985–2019). DHS, Demographic and Health Surveys.

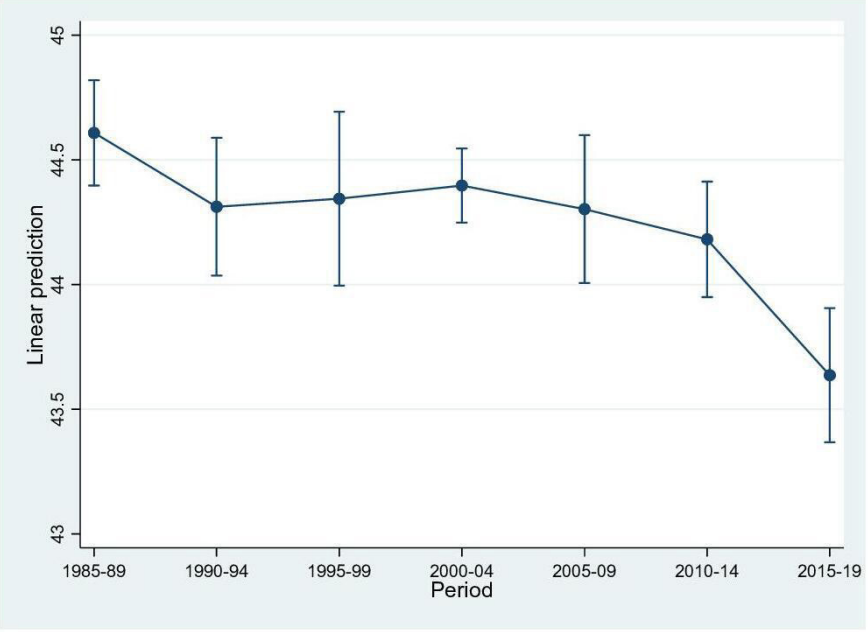

Figure 3 Predicted global trends in singulate mean age at menopause (SMAM) by survey period (DHS 1985–2019), with bootstrapped CIs. DHS, Demographic and Health Surveys.

We overcome this by calculating a truncated singulate mean age at menopause (SMAM). This measure is based on a demographic method that is used to calculate the singulate mean age at marriage,[6] a synthetic population-level measure that estimates the average age at marriage derived from the proportion of single persons in successive age groups. Here, we treat marriage like menopause, because menopause only occurs once and can be treated as an absorbing state, just like 'ever marriage'.

We therefore calculated the SMAM as:

$$A = 15 + \sum_{a=15-19}^{45-49} F_a * 5 \quad (1)$$

where F_a is the proportion of women who have not gone through menopause at age a. We then have the proportion of women who have not undergone menopause by age 50 years.

$$B = F_{45-49} \quad (2)$$

And estimate the proportion of those who are postmenopausal as:

$$C = 1 - B \quad (3)$$

The calculation of the number of person-years lived by the proportion of non-menopausal women is denoted as D

$$D = 50 \times B \quad (4)$$

The SMAM is then calculated as:

$$SMAM = \left(A - D\right) / C \quad (5)$$

In absence of data for older women, the resulting metric gives us a useful summary statistic for the observed distribution. We further tested the robustness of the distribution by conducting correlations with the prevalence of premature and early menopause for each survey. The correlation coefficients were −0.87 (p<0.001) and −0.71 (p<0.001) for premature and early menopause, respectively, demonstrating an excellent fit of the SMAM with these standard menopause measures.

Using survey-specific estimates of the prevalence of early and premature menopause, as well as the SMAM, we estimate global, regional and country-specific levels and trends. We also estimate bootstrapped confidence intervals (CIs) for all values using STATA V.17 which allows calculation of CIs for mean values across subcategories (eg, region, time) drawing on subsamples within the dataset.[36] The advantage of bootstrapping is that it allows a straightforward way to derive the estimates of standard errors (SEs) and CIs when the sample is not random and it is not feasible to calculate standard CIs. The regional averages included all values for each 5 years. We also present the marginal error effects to show the width of the CIs, which allows a more meaningful interpretation of the results.

Patient and public involvement

The study did not involve patients. The data come solely from demographic household surveys (DHS) collected by the United States Agency for International Development (https://dhsprogram.com/).

RESULTS

Due to demographic similarities and the small number of surveys collected in some areas, we combined countries into the following five regions: Central Asia; Latin America and the Caribbean; North Africa/West Asia/Europe; South and Southeast Asia; and Sub-Saharan Africa (table 1) (the list of countries is reported in the online supplemental appendix tables A1 and A2). We show both actual trends as well as the marginal effects

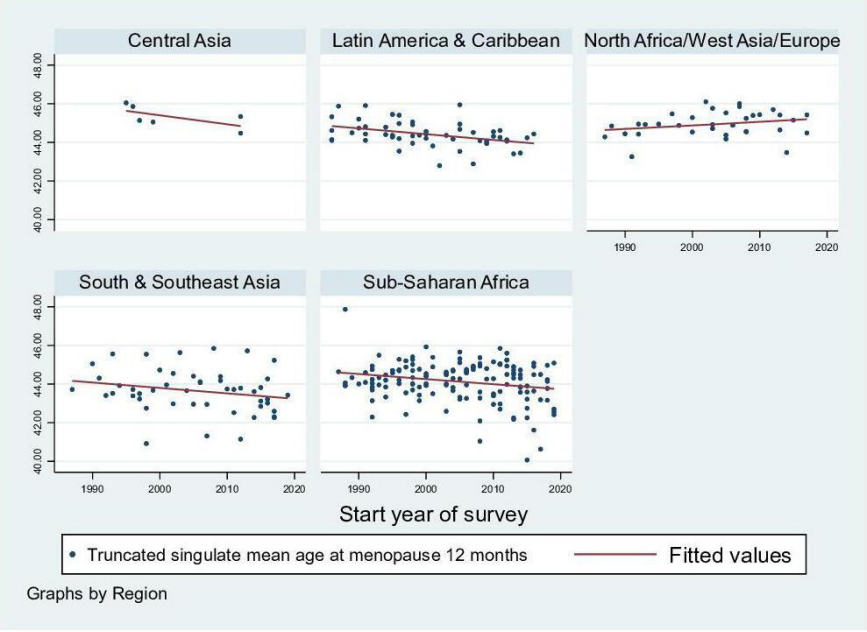

Figure 4 Regional trends in singulate mean age at menopause (SMAM) (DHS 1985–2019). DHS, Demographic and Health Surveys.

from the bootstrapped regression. The marginal effect communicates the rate at which *y* changes at a given point in covariate space, with respect to one covariate dimension and holding all covariate values constant. We believe that by simply showing the slope value at any point in the period of observation, we get a clearer idea of the estimated overall trends.

The data in table 1 show that premature and early menopause levels are highest in South/Southeast Asia (2.7% and 4.5%, respectively). These values are far ahead of other regions, where the next highest premature menopause prevalence is reported in Latin America and the Caribbean at 1.5%, and the next highest early menopause prevalence in sub-Saharan Africa at 2.4%. The lowest prevalences were in North Africa/West Asia/Europe (0.1% for premature and 1.4% for early menopause). At the national level, there is further variation in premature menopause prevalence, with values varying between 0% (Papua New Guinea) and 8.7% (South Africa). The variation is even greater for early menopause prevalence, which ranges between 0.7% in Gabon and 10.5% in Ethiopia (online supplemental tables A1 and A2). The single-year point data also show a considerable number of countries (16 out of 76 countries) with a prevalence of early menopause above 10% (data available on request). Despite the relatively high values in a few instances, both the premature and early menopause values fit within the ranges seen in the literature but suggest a higher prevalence than average for early menopause in particular.[10] Overall, we do not see a pattern of either high or low premature/early menopause by geographical or developmental region with countries consistently reporting high (eg, Indonesia) or low (eg, Jordan) values across time showing consistency in the estimates.

Figure 1 illustrates overall trends whereas figure 2 shows the actual underlying data including outliers. When looking at trends across time through predictions of the means and bootstrapped 95% CIs (figure 1), we see a stalling of early menopause prevalence and an increase in the prevalence of premature menopause over time, suggesting a move towards earlier ages of onset. Trends within regions across time show a slight increase in South and Southeast Asia and Latin America and the Caribbean, stalling for Central Asia and sub-Saharan Africa, and a decline for early menopause in North Africa/West Asia/Europe (figure 2) more in line with the literature on HICs.[14] In the case of the Asian region, the outliers across time represent Indonesia with consistently higher than regional average values, as well as Myanmar. In sub-Saharan Africa, a few countries (South Africa, Ghana and Mozambique) represented the outliers and dissonance with trend values.

Globally, SMAM shows a general decline with a temporary increase in the 1990–2004 period (figure 3). The SMAM varies by region (figure 4). In general, the highest mean age is reported in Central Asia (45.3 years) and the lowest in South and Southeast Asia (43.7 years) (table 1). Trends show a mild significant decline everywhere aside from North Africa/West Asia/Europe (which shows an increase) (figure 4), in line with the results on early and premature menopause trends (figure 2).

DISCUSSION

Our findings suggest that levels of menopause have not been stable across the last three decades and patterns vary across world regions. Among LMIC regions, there is a slight increase in early and premature menopause

prevalence and possibly an overall decline in the mean age at menopause, with the exception of North Africa/West Asia/Europe. While secular data from HICs might have led us to expect the same trends in LMICs, this study's observed secular trends indicate a different direction. Nutrition transitions, trends in age at first birth, as well as timing of puberty could all have a role in the trends we observe here. As pathways to menopause are influenced by epidemiological and socio-economic factors as well as biological differences, we might be witnessing a potential faster pace of ageing due to a higher burden of ill health and more reproductive life events for both high and low socio-economic groups in LMICs.[15 18] Increasing prevalence of early menopause has already been identified in Iran[37] (low socio-economic status) and Indonesia[30] (high socio-economic status). A possible explanation for stalling or increasing trends in the prevalence of early and premature menopause in some regions could be, as shown in previous research, that urban and more educated women are more likely to experience early and premature menopause.[30] This is happening at the same time as women of low socio-economic groups seeing a rise as well. However, further research is needed to understand how sociodemographic and epidemiological transitions might work differently in their impact on menopause across regions.[30]

We are not able to fully relate our findings with previous studies in LMICs beyond the few we mention due to the lack of research and data in the field. So far, we show different regional trends in line with what is available. There is also a discordant direction compared with the trends in the Global North,[14] which could be mainly due to differences in nutritional status and health conditions. The declining trends in premature and early menopause as well as the relatively lower levels in North Africa/Europe region are in line with the results in HICs showing consistency of trends. The increase in prevalence of early menopause mainly in Asia and sub-Saharan Africa could be a significant shift of reproductive periods mainly in light of declining age at menarche.[38] The trends are not as clear for the SMAM but there is still a significant declining trend in Asia and Latin America with an increase in North Africa/Europe. The next stage of research needs to focus on the determinants of the timing of menopause. Variations by residence, ethnicity and socio-economic differential would be a first starting point.

This study comes with limitations which start from the availability of data only up to the age 50 years, which we partially overcome with the use of the SMAM. Recall could be an issue which would need to be further tested. However, our initial checks did not show major inconsistencies beyond those reported.

In addition to some of the limitations in the calculations, as discussed by Flint,[14] data from surveys are affected by definitions of who is included in the numerator which restrict the criteria for inclusion and the sample being used. Menopause is variably defined, and the timing of data collection differs greatly across studies, which are often limited to single countries (eg, Finland, Taiwan, the USA[39 40]). This piecemeal approach in single countries, as well as lack of standardised data, has limited thus far our understanding of secular and global trends. The way forward would be a more systematic form of data collection such as a register or data collating exercise through GP offices or health workers which collects data at national level that is comparable across time and space. This is, however, a real challenge in low-resource settings, so we need to make the most of the precious available data, such as the DHS, and attempt to create a standard and international definition[14] (eg, use 12 months rather than 6 months from last menstrual period). Ultimately, given the expansion of the reproductive period, we could aim to push the age of the interviews in the DHS to the age of 55 years. We also call for more qualitative studies around the recall and cognitive interviewing on the age at last period in large surveys. The information is often discarded as of low value but as this study showed, a very simple question could go a long way towards the study of menopause on a comparative large scale.

This study calls for more research in this field, especially in LMICs where we need a greater understanding of menopause trends and their implications. The mental and physical consequences of early and premature menopause could be significant in settings where fertility is part of cultural acceptance. There is a need to converge epidemiological, biological and social sciences in identifying the linkages between reproductive histories, menopause timing and socio-economic/bio-economic/economic differentials. Future studies could look at both macro and micro differentials trying to link structural (eg, level of development, health systems/health expenditure) as well as individual factors (eg, timing of menarche). Above all, with an increasing availability of biometrics (eg, weight and height) and biomarkers (eg, blood levels, grip strength), we need to link cohort information to timings of menopause to better understand the mechanisms at play.

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Contributors TL conceived the study, run the methodology, wrote the first draft, finalised the paper and obtained the funding. LB contributed to the analysis, the drafting, the preparation of the data and calculation of the indices. AG conceived the SMAM and contributed to the analysis, drafting and finalisation of the paper. TL is the guarantor and accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. All data are available upon request from the DHS macro website.

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