Introduction
The onset of menopause often signals an unwelcome transition in the lives of many women. According to Palacios et al (1), although the timing of natural or spontaneous menopause may vary genetically, ethnically, and geographically, the latter variations are found in the natural menopausal age of major regions in the world including Europe (50.1-52.8 years), North America (50.5-51.4), Latin America (43.8-53), and Asia (42.1-49.5).

The age of the onset of menopause is suggested to significantly affect women's health. This is corroborated by UK Biobank data which represented that earlier menopausal age (<47 years) is independently correlated with the higher incidence of cardiovascular diseases (CVDs) in later life (2). Additionally, a significant association exists between lower menopausal age, longer duration of postmenopausal period, and a shorter period between menarche and menopause, with the risk of CVD or CVD-related mortality (3-5).

Early menopause may occur due to medical interventions or genetic diseases although some social determinants are significantly related to the onset of natural menopause. These social determinants include education (6-8), oral contraceptive use (6-8), employment (6), smoking (6-8), body weight (6-8), alcohol consumption (6,8), self-rated health (6), physical activity (6-8), younger generation (7), early menarche (7,8), age at first birth (7), parity (7,8), an experience of severe food shortage (7), socioeconomic status (8), and diet (7,8). What is missing from the list is the residential factor, especially the rural-urban factor, even though numerous direct and indirect studies have focused on the rural-urban difference in the onset of natural menopause.

Given the undesirable relation of menopause with women’s health, this review aimed to establish a correlation between the rural-urban factor and natural menopausal age. Such findings will be useful in the formation and implementation of health policies that respond to the needs of rural and urban women.

Methods
A comprehensive literature search was done electronically for scientific publications written in English or bilingual (English with one other language) by using databases such as MEDLINE, PubMed, and Google Scholar. The key search terms were “menopause”, “age”, “urban”, and...
"rural" as the scope of the review was to determine the association between rural and urban residences with the age of the natural onset of menopause. In addition, the search covered academic publications from 1984 to 2017. Once the association between rural-urban and the age of natural menopause was established, the literature search was expanded to explore the literature for some correctable confounding factors by focusing on smoking habit, physical activities, and the body mass index (BMI) between rural and urban populations with stratification of the countries where the studies on the age for the onset of natural menopause originated.

**Results**

Our literature search uncovered 13 research articles that shed light on rural-urban differences in natural menopausal age, including 6 from India, 3 from Iran, 2 from Europe, as well as and 1 from China, Mexico, and South Africa, respectively (Table 1).

**Regional Variation in Rural-Urban Differences in Menopausal Age**

Of all the 13 studies on menopausal age, nine were from the Asian region including India (n = 6), Iran (2), and China (1) while only 2 studies were found from Europe including Spain (1) and Poland (1), respectively. Both Africa and North America contributed one publication each.

Nine of the studies indicated that the rural population begins their natural menopause earlier than their urban counterparts (10,11,14,16-21) with statistically significant differences in about half of these findings (10,19-21). The other four studies, however, reported contradictory findings (9,12,13,15) with one showing a significant level of difference (15). Of the nine studies that suggested an association between rural residency and earlier menopause, eight were from Asia. This association is in contrast with the majority of findings in the non-Asian regions except for Mexico (10). In these regions, the rural population appeared to experience later onset of natural menopause compared to their urban or semi-urban counterparts. Therefore, it is apparent that rural-urban differences in the age for the onset of natural menopause have regional variations.

**Discussion**

The difference in the age for the onset of natural menopause between the rural and urban population is apparent in all studies included in our review, with statistically significant findings in some of the studies. Furthermore, our review of the literature showed that women living in rural areas of Asia are more likely to begin their menopause earlier than their urban counterparts. Therefore, it is believed that it is justifiable to suggest that “rural” and “urban” factors may play a central role in early- or late-onset menopause age. However, it must be noted that “rural” or “urban” residence is not clearly defined in any of the analyzed studies. Indeed, the term “rural” or “urban” can be a multidimensional classification that can take into account economic activities, geographical dimensions, and population density (22).

Although the reasons for the rural-urban variation in menopausal age have not been clearly identified in the reviewed literature, some studies have addressed this issue. Based on the report of a study in Mexico, the genetic factor was considered as the main determinant (10) although another study indicated that the cause is multifactorial, including BMI, age, and environmental context (13). Taking into account the significant association between rural residency and low BMI with earlier menopausal age, the findings of a study in Iran demonstrated that rural-urban socioeconomic differences are the responsible factor in this regard (21). This conclusion was mirrored by the UN data on rural women which indicated that women living in rural areas are faced with numerous constraints including access to affordable, adequate, and holistic health services that address physical, mental, and emotional well-being (23).

Overall, the urban population has better general health outcomes, even those who may live within the same poverty line as those in the rural area. The possible reason for this “urban health advantage” is the proximity of wealth and poverty within cities which bring benefits to those less well-off. More importantly, the urbanites also enjoy higher levels of social support and greater social cohesion, more access to the necessities of life, more health-friendly environment, along with more politically and socially mobilized health resources (24). For example, life expectancy at birth is substantially lower for both American males and females in rural areas compared to the urban areas. This disparity was associated with mortality and/or morbidity from both communicable and non-communicable diseases, as well as physical or mental illnesses conditions greatly influenced by access to quality health care (25). However, rural-urban health disparities cannot be solely observed due to the effect of rurality. It may be the result of a combination of multiple factors that are deficient among the rural population, including socioeconomic status, service availability, personal risk levels, environmental and occupational conditions, transportation conditions, and ethnicity (26).

It was further speculated that there may be other underlying factors that correlate with the rural-urban difference in the natural menopausal age since it may have regional variations, especially between Asian and non-Asian regions.

**Possible Correlates of Rural-Urban Differences in Natural Menopausal Age**

1. **Smoking Habit**

The prevalence of tobacco smoking among rural and urban women in Asian and non-Asian populations can...
Table 1. Summary of Articles on Age for the Onset of Natural Menopause Among Rural and Urban Women

| First Author/Year | Country     | Study Design                  | Sample Size Rural/Urban | Comparison | Rural          | Urban         | Significance Level |
|-------------------|-------------|-------------------------------|-------------------------|------------|----------------|---------------|-------------------|
| Walker (9)        | South Africa| Cross-sectional               | 1850/1255               | Mean       | 49.5±4.7       | 48.9±4.2      | Not stated        |
| Malacara (10)     | Mexico      | Cross-sectional               | 7632                    | Mean (3 areas) logistic regression | 47.3          | 49.0          | 47.0          | P < 0.001*        |
| Mohammad (11)     | Iran        | Cumulative distribution (NHS) | 8194                    | Median     | 49.2           | 49.9          | 95% CI:1.00066    |
| Kaczmarek (12)    | Poland cohorts | 1. 1948 survey            | 7183                    | 1. Mean 2. Mean 3. HR Living environment | 49.28         | 50.49         | 49.94          | 50.21          | 0.93 (0.87-1.01) P < 0.52 |
| Cristina (13)     | Spain       | Pooled data from 2 research projects | 103 rural 744 semi-urban 295 urban | Median | 52.07 (rural) | 51.9 (semi-urban) | 51.23 (urban) |
| Kaur (14)         | India       | Cross-sectional              | 110/70                  | Mean       | 48.22 (2.47)       | 49.30 (2.80)       | P<0.001* Multivariate analysis 7.1% variance |
| Dasgupta (15)     | India       | Observational cross-sectional | 250/250                 | Mean       | 48.56 (2.27)       | 49.56 (4.12)       | P<0.0667        |
| Sagdeo (16)       | India       | Observational cross-sectional | 300,000                 | Mean       | 48.0 (4.4)        | 48.5 (4.4)        | Not stated       |
| Lewington (17)    | China       | Baseline data of CKB blood based prospective cohort | 50/50                  | Mean       | 48.28           | 49.78          | Not stated       |
| Nidhi Sagar (18)  | India       | Comparative study            | 100                     | <48 y       | 84.8% (15.2%)     | 51.9% (48.1%)     | P<0.001*         |
| Murugan (19)      | India       | Cross-sectional door to door survey | 4898                      | Median      | 50.3           | 50.7          | Adjusted HR 1.09 (1.01-1.18) P<0.01* Adjusted OR 1.35 (1.12-1.62) P<0.01* |

Note. NHS: National Health Service; CI: Confidence interval; HR: Hazard ratio; CKB: China Kadoorie Biobank; OR: Odds ratio.
*Statistically significant.

be the contributing factor to the difference in the age for the onset of menopause. Several studies support the notion that the earlier onset of age at natural menopause experienced by the rural population in the Asian region is correlated with tobacco smoking. For example, the prevalence of smoking among rural Indian women population was more than five times that of their urban counterparts (27). However, 2010 data from China appeared to contradict the situation in India, where smoking was equally prevalent among rural and urban women born in the 1930s, and significantly higher among the urban women born in the 1940s onward. Further, smoking prevalence among males living in the rural area was significantly higher than their urban counterparts with a more remarkable difference among the older generation (28). Therefore, it can be assumed that rural Chinese women of the older generation have significantly higher exposure to second-hand tobacco smoke compared to their urban counterparts. Furthermore, Esmaeilzadeh et al (29) reported a higher rate of smoking among women living in the rural than the urban setting in Iran (6.9% vs. 15.1%, P<0.001).
Contrary to the Asian countries, four European countries (i.e., Finland, Germany, Italy, and Spain) were found to have more current smokers among the urban population compared to the rural population with an age-standardized odds ratio at 1.56 (95% CI = 1.48-1.66), as well as the age and education standardized odds ratio at 1.47 (95% CI = 1.38-1.55) for Spain (30). In contrast, a Polish study (31) of three birth cohorts (those born before 1940, between 1940 and 1960, and 1961-1979) demonstrated that rural residency is associated with a nearly two-fold increase in smoking. This may well reflect the finding that, similar to the Asian countries, the mean menopausal age for Polish women is lower among rural residents in the early cohort (1948) although the later cohorts revealed the opposite (1967) or no significant difference (200-2004).

The connection between smoking and the early onset of age at natural menopause was also observed in the African region. In South Africa, earlier menopausal age among urban women was correlated with the findings that the south African urban youths were more likely to smoke (OR = 1.39, 95% CI = 1.09-1.75) compared to their rural counterpart (14,32). No literature was uncovered to correlate smoking with the onset of age at natural menopause in Mexico.

In summary, the onset of menopause is earlier in either rural or urban settings, where smoking is more prevalent. Therefore, smoking may be one of the correlates of the difference in natural menopausal age between the rural and urban populations.

2. Physical Activity
High physical activity may be associated with a lower age for the onset of natural menopause. In the Asian region, a significantly higher proportion of women living in the rural settings engaged in high physical activity compared to their urban counterpart, with the odds ratio of 3.61 for rural (95% CI = 2.36-5.54) in India (33), 71.4% rural vs. 17.7% urban (P < 0.01) in China (34), and 71.2% rural vs. 44.7% (P < 0.0001) in Iran (29). These appear to be associated with lower natural menopausal age among rural women compared to their urban counterparts in India, China, and Iran (Table 1).

In contrast with the Asian studies, lower menopausal age in the urban area compared to the rural area of South Africa is not compatible with the findings by Peer et al that indicate lower physical activity among the urban population compared to their rural counterpart (OR: 1.45, 95% CI: 1.12-1.89) (32) Similar observation was made for Spain as less physical activity seems to correlate with lower natural menopausal age. Compared to their rural and urban counterparts, the semi-rural women in Spain who were reported to be engaged in higher physical activity registered the highest age at natural menopause (35). However, corroborating the Asian studies, a higher age at natural menopause among those living in the rural areas of Poland appears to be associated with significantly less leisure-time inactivity (36).

In general, there is a strong indication of physical activity contributing to the difference observed in the onset of age at natural menopause between urban and rural populations.

3. Basal Mass Index
In India, China, and Iran, higher menopausal age among the urban women compared to their rural counterparts appeared to correlate with a higher BMI. A marked difference in BMI was reported between the urban and rural female population in India where the rate of overweight and obesity among the urban women was 47.6% and 16.4%, respectively, while that of the rural women was 11.3% and 2.2%, respectively (37). In addition, Jayamani et al (33) reported the odds ratio of urban overweight/obese among the women population as 5.55 (95% CI = 3.33–10). Similarly, a study from Iran (39) reported an adjusted obesity odds ratio at 1.54 (95% CI = 1.31-1.80) for urban adults where the odds ratio for females was 1.47 (95% CI = 1.26-1.72) (38). However, two contradictory observations were made in China. Using a stratified cluster sampling method, an earlier study showed that the prevalence of obesity is higher in urban areas. More precisely, 10.2%, 6.8%, and 6.5% were reported among women living in the city, township, and rural areas, respectively (P < 0.005) (39). This contradicts by a later report based on the data extracted from nationwide breast cancer screening of China which revealed a significantly higher prevalence of overweight/obesity among the rural Chinese women compared to the urban Chinese women (P < 0.001) (40).

Marked differences in BMI between rural and urban dwellers were not observed in the non-Asian countries. A study from Mexico found that living in the urban area (OR = 5.90, P < 0.007) is independently associated with obesity in older adult individuals (41). Similarly, the rate of overweight/obesity was independent of the dwelling area although higher waist circumference (more than 88 cm) was more prevalent among rural dwellers compared to their urban counterpart (P < 0.05) (42). Furthermore, the findings of a study of the populations in 10 European countries, including Spain, demonstrated no difference in the prevalence of overweight and obesity between rural and urban areas. Moreover, the analysis of compounding factors such as gender, age, education, or income levels did not reveal additional rural-urban variations (43). Later, it was reported that in 20 European countries, including Poland, overweight and obesity rates are significantly higher among those who live in rural areas compared to those of the urban areas (44).

In summary, although the correlation between BMI and the menopausal age cannot be rationalized in non-
Asian countries, there is a clear indication of a connection between higher BMI and higher menopausal age in Asian countries, suggesting BMI as one of the contributing factors for earlier menopause among the rural women (Table 1).

Long-term Health Risks of Early Menopause
The menopausal age can be considered as an important factor in stratified risk assessment for CVDs for women. The risk of CVD in women was suggested to increase by a decrease in menopausal age. The comparison among women who reached menopause at age 50-51 years revealed that the risk of CVD was 55%, 30%, and 12% higher among women who reached menopause at age less than 40, 40-44, and 45-49 years old, respectively. In addition, these risks were reported to intensify before 60 years of age (45).

Furthermore, women with early menopause (less than 47 years old) are 1.8, 1.7, and 1.6 times more likely to have osteoporosis at 77 years of age, fragility fracture, and risk of mortality, respectively, when compared to those who experienced late menopause (47 years old or older) (46). Additionally, recently published data from a large prospective cohort study highlighted that the mean natural menopausal age (<47.4 years) was significantly linked to a 19% increase in the risk of dementia (47).

Limitations
A meta-analysis of the results compiled from the reviewed studies was not done due to the following reasons:
1. There were some disparities with regard to the method used among the studies. Seven studies used an observational cross-sectional study design (9, 10, 14-16, 19, 20) and only one study used the comparative study design but the sample size was rather small (18).
2. The sampling frame was different among the studies.
   Some data were taken from active collections, either from the community or hospital settings while some were extracted from other sources such as previous menopause-related research projects or the biobank. The pooled data yielding good sample size were extracted from retrospective or prospective research projects that were not related to menopause (11-13,17,21). Only seven studies had a considerably large sample size (9-13,17,21).
3. The selection method was not stated in some articles although most of the studies used the convenient sampling technique. In addition, the women were enrolled from randomly selected residential areas only in a study in Poland (12).
4. There were variations in the age inclusion criteria among the studies. The age range varied between 10 and 44 years old with the lowest age at 29 (19) and the highest age at 70 (14). One report had no record of the highest participant’s age in its data analysis (17).
5. The inclusion criteria related to the type of menopause was inconsistent among the studies. Surgical menopause was included in some studies (16-18,21) as the purpose of their study was not just to determine the menopausal age among the residents.
6. The women who had natural menopause at an older age were excluded in some studies. In these studies, premenopausal women who reached their menopause at an older age (>55) were excluded in the cross-sectional sampling (13,18).
7. The menopausal age, mean (9,15-18), median (11,12), both mean and median (14), the hazard ratio (12), or the logistic regression of the means (10) were used for comparison. In two Indian studies, the Chi-square test was used to analyze the correlation between menopausal age groups and their place of residence (14,15).

Conclusions and Recommendations
Our analysis of the available data strongly suggested that rural-urban differences in menopausal age have regional variations. Asian women living in rural areas were more likely to reach menopause earlier than their urban counterpart and this association was not replicated in the non-Asian region. However, rurality by itself may not be the sole predisposing factor for early menopause. Smoking, high physical activity, and low BMI are three variables that may have a significant correlation in this regard. The socioeconomic disparity, as another possible factor, was not determined in this study.

It is well proven that natural estrogen provides both cardio-protective and bone protective effects. Therefore, all women should benefit from the endogenous estrogen by a natural delay in the menopausal age for reducing the risk of osteoporotic fractures, as well as cardiovascular morbidity and mortality. To make this possible, the improvement of social, economic, and environmental conditions of a given community should focus on reinforcing programs and improving physical facilities to allow women better access to a healthier lifestyle including more physical activities, zero smoking, and healthy BMI. Further research should address the health benefit of a delay in natural menopause. It would also be interesting to have an on-going study that evaluates the effect of engaging in regular exercise, maintaining/achieving a healthy weight, or reducing weight in obese/overweight women and smoking cessation on the onset of menopause.

Conflict of Interests
Authors declare that they have no conflict of interests.

Ethical Issues
Not applicable.

Financial Support
We do not receive any funding for this project.
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