Effect of aging, menopause, and age at natural menopause on the trend in body mass index: a 15-year population-based cohort

Seyed Ali Montazeri, M.D., M.P.H.,[a] Fahimeh Ramezani Tehrani, M.D.,[a] Razieh Bidhendi Yarandi, M.Sc.,[a,b] Hadi Erfani, M.D.,[a,c] Mohammad Ali Mansournia, M.D., Ph.D.,[b] and Fereidoun Azizi, M.D.[d]

[a] Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [b] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [c] Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas; and [d] Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Objective: To observe the effects of menopause, age at natural menopause (ANM), and aging on the trend in body mass index (BMI).
Design: Prospective cohort with a 15-year follow-up of 929 women. Data obtained from the Tehran Lipid and Glucose Study.
Setting: Not applicable.
Intervention(s): none.
Participant(s): Of women participating in the Tehran Lipid and Glucose Study, 929 who were reproductive during the study and menopaused at the last follow-up were included. Anthropometric data were measured repeatedly every 3 years, and the trend in BMI, associated with menopause and ANM, was tested using the generalized estimating equation.
Main Outcome Measure(s): Body mass index in each follow-up session.
Result(s): The adjusted model of the generalized estimating equation illustrates that BMI increases by age ($\beta = 0.16$) and menopausal status ($\beta = 1.11$). It also shows that women with higher ANM experienced a decreasing BMI ($\beta = -0.03$) compared with women with lower ANM. The interaction term of menopause and time (menopause × time) has a negative effect on BMI; that is, the usual increase in BMI after menopause is attenuated by time. ($\beta = -0.4$, 95% confidence interval −0.6, −0.3).
Conclusion(s): Menopause and aging are independently correlated with increasing BMI. The trend in BMI, however, depends on the ANM of study participants: women with higher ANM than mean ANM of our population (i.e., 49 years) face a decreasing BMI compared with those with lower ANM. (Fertil Steril® 2019;111:780-6. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Age at natural menopause, body mass index, interrupted time series analysis, menopause, obesity

It is well understood that body weight increases with age (1). Generally, this increase is greater in women compared with men (2). Moreover, obesity is more common in women than in men. This worldwide health issue might get worse after menopause, when abdominal fat content increases even further (3, 4). Obesity, estrogen deprivation, and other hormonal changes secondary to menopause cause several adverse cardio-metabolic consequences that are correlated with obesity (5). Thus, knowledge of the association among aging, menopause, and obesity is of great importance.

Unfortunately, there is no consensus on the exact association of aging, menopause, and obesity. Some studies reported no significant difference in obesity between premenopausal and peri-/postmenopausal women and concluded that aging was the most important indicator in obesity (6–8). Nevertheless, other researchers revealed an increase in the prevalence of obesity, independent of aging, in peri-/postmenopausal women

Received July 30, 2018; revised December 6, 2018; accepted December 19, 2018.
S.A.M. has nothing to disclose. F.R.T. has nothing to disclose. R.B.Y. has nothing to disclose. H.E. has nothing to disclose. M.A.M. has nothing to disclose. F.A. has nothing to disclose.
The data of this study was derived from the TLGS Study, which was funded by Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences (grant no. 2673; ethics code IR.SBMU.ENDOCRINE.1396.408.
Reprint requests: Fahimeh Ramezani Tehrani, M.D., Research Institute for Endocrine Sciences, 24 Parvaneh, Yaman St., Velenjak, Tehran 19395-4763, Iran (E-mail: ramezani@endocrine.ac.ir).

Fertility and Sterility® Vol. 111, No. 4, April 2019 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.12.017

compared with premenopausal ones (9, 10). These different findings could give us a deeper insight into the effects of age at natural menopause (ANM) on changes in obesity.

Age at natural menopause, which may have a broad range of 40–60 years in a population (11, 12), is mainly dependent on genetic background and is influenced by environmental factors and different lifestyles (13). Despite a positive association that was found between body mass index (BMI) in premenopausal years and ANM in some studies (14, 15), it has not been observed in others (16, 17). To the best of our knowledge, few, if any, researchers have explored this important association in a reverse direction; that is, they mainly explored the impact of ANM (as a dependent variable) on further obesity and BMI (as independent variables).

Repeated measurements of BMI throughout the reproductive lifespan to the postmenopausal period in women who were participants in a 15-year population-based cohort, the Tehran Lipid and Glucose Study (TLGS), enabled us to explore whether ANM, besides menopause and aging, is associated with BMI changes after menopause.

MATERIALS AND METHODS

Design

This is a population-based prospective cohort with 15 years of follow-up conducted within the framework of the TLGS, which is an ongoing (since 1998) cohort study of 15,000 participants from an urban population aged ≥3 years (18). Demographics, reproductive variables, and various risk factors for noncommunicable diseases have been collected at baseline and in consecutive 3-year follow-up sessions. Trained interviewers and examiners have filled out a comprehensive questionnaire; have conducted a general physical examination; and have taken blood samples at each face-to-face visit, following obtainment of informed written consent.

Participants

The present study was initiated in 1998. Four follow-ups with 3-year intervals for each participant are included in this study. Of a total of 2,412 women with regular menstrual cycles in the TLGS cohort, those with diagnosis of any type of cancer, surgical menopause (i.e., history of either hysterectomy or bilateral oophorectomy), or history of hormone replacement therapy during follow-ups were excluded from the study (n = 959). Additionally, 524 women who had missing data or who had not been present at follow-up sessions were excluded. In our study, finally 929 nonmenopausal women aged ≥30 years at initiation of the study who reached natural menopause by the end of the study were included. Reproductive variables, including menstruation (age at menarche, menstrual interval, and age at menstrual cessation), marital status, and parity were collected at each follow-up. All women were menopausal by the end of the study period.

Measurements

At each visit, body weight was measured with a digital scale (Seca 707) when participants were minimally clothed. Height was measured in centimeters in the standing position while the shoulders were in normal alignment. Waist and hip circumferences (WC and HC) were measured in centimeters with a tape meter without pressure to the body surface.

Definitions

Menopause was defined as the permanent cessation of menstruation for ≥12 consecutive months due to ovarian reserve depletion, without any history of surgical or iatrogenic menopause. This was defined and reassessed during interviews at each follow-up session. Age at menarche was considered as the age (in years) at first menstruation for each participant. Parity was defined as the number of pregnancies, regardless of the outcome (i.e., live birth, abortion, or stillbirth). Age at natural menopause was defined as the age at which the above-mentioned menopause had occurred. Centered ANM was calculated as one's ANM minus the mean ANM of the population; each woman then was placed in one of the following categories according to her centered ANM: higher ANM (i.e., her ANM ≥ mean ANM of the population); or lower ANM (i.e., her ANM < mean ANM of the population [i.e., 49 years]).

Body mass index was calculated as weight divided by height in meters squared (kg/m^2). On the basis of BMI, participants were considered as normal weight (BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2), or obese (BMI ≥ 30 kg/m^2). Waist-to-hip and waist-to-height ratios were calculated as WC divided by HC and height, respectively. Abdominal obesity was defined as WC ≥ 95 cm, according to the national cut-off values (19). All participants were categorized as either ever- or never-smokers.

Statistical Analyses

Descriptive statistics for the follow-up sessions of the study were reported as mean ± SD and percentage for categorical variables. Parametric Student *t* test or nonparametric Mann-Whitney *U* test were applied to test the difference of characteristics variables between menopaused vs. nonmenopaused women, appropriately.

In addition, to analyze longitudinal data in which each subject's measurements are repeated over time, we used a generalized estimating equation (GEE) model, which accounts for correlations within subjects through a working correlation matrix. Actually, the GEE approach provides an advanced method of regression parameters estimation, which can overcome the weaknesses of classic methods such as repeated-measures multivariate analysis of variance. It enables researchers to accurately estimate the effect size in case of incomplete data (missing variables in some repeated measures), which is common in cohort studies. Interestingly, GEE models can provide comparable results to those of other repeated-measure analyses done on complete datasets (20). Moreover, GEE provides modified parameter estimations to deal with confounding variables (21).

In this study, to estimate the effect of menopause (being menopaused vs. nonmenopaused as the reference group) over time, a GEE model was applied. Then, an exchangeable

working correlation matrix that accounts for correlations within subjects was implemented. First, a crude GEE regression model, which only consisted of menopause status, was fitted to find the overall effect of being menopaused. Secondly, an adjusted (trend) model including age (continuous), menopausal statuses (categorical), centered ANM (continuous), time (i.e., follow-up session as an ordinal variable), and the interaction term of time and menopause status (time × menopause status) was applied.

Adjusted (Trend) Model

$$\begin{aligned}&E(\text{BMI}|\text{Age}, \text{Menopause Status}, \text{Centered ANM}, \text{Time})\\&= \beta_0 + \beta_1 \text{Age} + \beta_2(\text{Menopause Status})\\&\quad + \beta_3(\text{Centered ANM}) + \beta_3(\text{Time})\\&\quad + \beta_4(\text{Menopause Status} \times \text{Time})\end{aligned}$$

The significance level was set at $P<.05$ and the confidence interval (CI) at 95%. Statistical analyses were performed using IBM SPSS Statistics for Windows and STATA statistical software.

Ethics Approval

The ethical review board of the Research Institute for Endocrine Sciences approved the study protocol and execution of the study.

RESULTS

Table 1 shows the characteristics of the study population at baseline and follow-up sessions. The mean ± SD of age and BMI at the baseline of the study are 43 ± 5 years and 29 ± 5 kg/m^2, respectively. Mean age at menarche and ANM are 14 ± 2 and 49 ± 4 years, respectively.

The results of GEE models with different imputed factors (crude and trend models) are depicted in Table 2. The crude model shows that menopause has a positive effect on BMI; that is, mean BMI of menopausal women was 0.9 (95% CI 0.8, 1.0) higher than BMI of the premenopausal ones ($P<.001$). The trend model illustrates that BMI increases by age ($\beta = 0.16$) and menopausal status ($\beta = 1.11$); this model also shows that women with higher ANM (i.e. whose ANM was ≥49 years) experienced a decreasing BMI ($\beta = -0.03$) compared with women with lower ANM ($P<.05$). The interaction term of menopause and time (menopause × time) has a negative effect on BMI; that is, the usual increase in BMI after menopause is attenuated by time ($\beta = -0.4$, 95% CI −0.6, −0.3) (Table 2). This finding is further clarified in Figure 1, which shows the trend in BMI of participants at follow-up sessions. In this figure, the BMI level in menopaused women is higher than that of nonmenopaused ones. The trend in BMI level is decreasing in menopaused women, whereas nonmenopaused women faced an increasing trend in BMI.

TABLE 1

Descriptive characteristics of the study participants.

Characteristic	Baseline	1st follow-up		2nd follow-up		3rd follow-up		4th follow-up
	No	No	Yes	No	Yes	No	Yes	Yes
No. of participants	929	752	177	511	394	174	685	929
Age (y)	43 ± 5	45 ± 4	51 ± 5[a]	46 ± 4	52 ± 5[b]	48 ± 4	54 ± 4[c]	54 ± 4
BMI (kg/m^2)	28.8 ± 4.6	29.1 ± 4.5	30.6 ± 4.7[a]	29.3 ± 4.8	30.1 ± 4.8[b]	29.5 ± 4.8	29.9 ± 5.1	29.9 ± 4.6
HC (cm)	106 ± 9.1	106 ± 9	109 ± 10[a]	106 ± 9.5	107 ± 10.1	103 ± 8.5	104 ± 9.2[c]	103 ± 9.8
Weight (kg)	70 ± 12	71 ± 12	74 ± 12[a]	73 ± 12	73 ± 12	72 ± 12	73 ± 12	73 ± 13
WC (cm)	90 ± 11.3	92 ± 11.5	99 ± 11[a]	92 ± 11.7	96 ± 12.2[b]	96 ± 10.7	98 ± 11.5[c]	98 ± 12.4
Waist/hip ratio	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.3
Waist/height ratio	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Systolic blood pressure (mm Hg)	119 ± 18	115 ± 16	122 ± 20[a]	118 ± 18	121 ± 19[b]	118 ± 15	122 ± 19[c]	117 ± 16
Diastolic blood pressure (mm Hg)	79.3 ± 10	76 ± 9	77 ± 11[a]	78 ± 11	79 ± 11[b]	78 ± 10	80 ± 11[c]	79 ± 10
FPG (mg/dL)	99 ± 34	110 ± 41	109 ± 40[a]	99 ± 25	109 ± 29[b]	81 ± 29	81 ± 29	90 ± 29
HDL-c (mg/dL)	53 ± 12	45 ± 11	45 ± 12	41 ± 10	42 ± 11[b]	44 ± 11	44 ± 11	48 ± 12
LDL-c (mg/dL)	122 ± 37	131 ± 35	139 ± 34[a]	123 ± 31	133 ± 33[b]	116 ± 32	130 ± 31[c]	122 ± 34
Triglycerides (mg/dL)	164 ± 89	163 ± 95	189 ± 144[a]	164 ± 108	175 ± 97[b]	150 ± 81	177 ± 100[c]	162 ± 92
Total cholesterol (mg/dL)	207 ± 41	207 ± 40	221 ± 46[a]	195 ± 36	209 ± 39[b]	190 ± 37	208 ± 38[c]	203 ± 39
Overall characteristics								
Age at menarche (y)					14 ± 2			
Age at natural menopause (y)					49 ± 4			
Parity (IQR)					3 (2%)			
No. of children (IQR)					2 (0)			
Ever smoking					63 (7%)			
Education[d]					361 (41%)			

Note. Variables are reported as mean ± standard deviation or number (percentage) or interquartile range. No = nonmenopaused; Yes = menopaused. BMI = body mass index; FPG = fasting plasma glucose; HC = hip circumference; HDL-c = high-density lipoprotein-cholesterol; LDL-c = low density lipoprotein-cholesterol; WC = waist circumference.

[a] Mean difference of variable in group menopause vs. nonmenopaused was significant at 1st follow-up.

[b] Mean difference of variable in group menopause vs. nonmenopaused was significant at 2st follow-up.

[c] Mean difference of variable in group menopause vs. nonmenopaused was significant at 3st follow-up.

[d] Equal or more than 12 years of study (vs. lower than 12 years of study).

Montazeri. Age at natural menopause and BMI. Fertil Steril 2018.

TABLE 2

Results of GEE models showing the effect of menopause on BMI by adjusting confounding factors.

Model/parameter	Mean BMI regression coefficient (95% CI)	*P* value
Crude model		
Menopause (yes vs. no)	0.90 (0.80, 1.0)	< .001[a]
Adjusted (trend) model		
Age (y)	0.16 (0.11, 0.21)	< .001[a]
Menopause (yes vs. no)	1.11 (0.64, 1.59)	< .001[a]
Centered ANM	−0.03 (−0.07, −0.001)	.045[a]
Time	0.03 (−0.14, 0.21)	.696
Menopause × time	−0.45 (−0.61, −0.30)	< .001[a]

Note. Centered ANM = age at menopause minus mean ANM of the population (i.e., 49 years). Crude model: the effect of menopause status (premenopause as the reference group). Adjusted (trend) model: effect of age, menopause status, centered ANM, and interaction term of menopause status × time (time = follow-up sessions every 3 years). Regression coefficient (95% CI) and *P* value obtained from the GEE model, which showed mean difference of BMI.

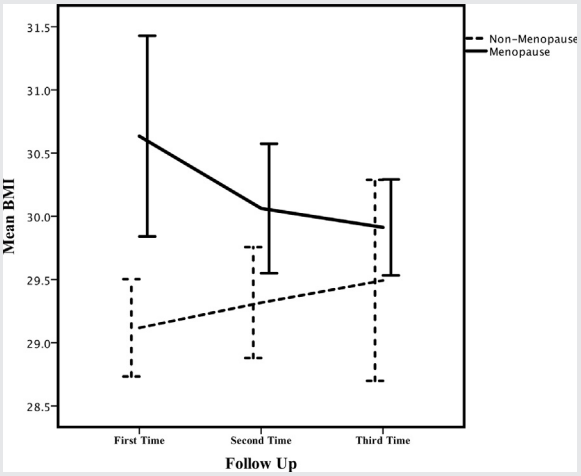
[a] Significance level < .05.

Montazeri. Age at natural menopause and BMI. Fertil Steril 2018.

DISCUSSION

In this population-based prospective cohort study with 15 years of follow-up, we have demonstrated that aging and menopause are independently connected to future increases in BMI, changes that were mainly dependent on ANM; the higher the ANM in comparison with mean ANM of our population (i.e., 49 years), the lower the future BMI. In other words, women with higher ANM face decreased BMI after menopause, the extent of which is positively proportional to the difference between their ANM and mean ANM of the population. On the other hand, women with lower ANM face increasing BMI after menopause, independent of menopause event. Results of the trend model also show that the typical increase in BMI (crude model) after menopause is attenuated by 0.4 kg/m^2 by time (follow-up session, every 3 years) in menopausal women compared with premenopausal ones.

FIGURE 1



Mean and confidence interval for observed BMI by menopause status at first, second, and third follow-up sessions.

Montazeri. Age at natural menopause and BMI. Fertil Steril 2018.

Recent genetic studies concluded that ANM might be determined mainly in the genes with less contribution of environmental and lifestyle factors (22, 23). It seems that the relative constant ANM for each woman, as an independent variable, could influence further changes in BMI during her lifespan. To the best of our knowledge, this prospective effect of ANM on BMI has yet to be documented in the literature.

There are, however, several studies on the association of BMI (independent) and ANM (dependent). Some of these studies reported a positive correlation (14, 15, 24), concluding that higher BMI is associated with higher ANM; whereas others, including the Framingham Heart Study (25), concluded no significant association (16, 26, 27). Morris et al. (14) in the Breakthrough Generations Study, a cross-sectional study in which 27% of women were overweight or obese, concluded that higher BMI was correlated to higher ANM. They showed that ANM in women who were underweight, normal, overweight, and obese at age 40 years was 52 (interquartile range [IQR] 50–54), 52 (IQR 50–55), 53 (IQR 50–55), and 53 (IQR 50–55) years, respectively. However, they used recall-based weight and height to calculate BMI. A cohort study by Akahoshi et al. (15) showed that the BMI at age 40 years was related to higher ANM in Japanese women. They concluded that women of the upper 25% BMI had higher ANM (50.4 ± 2.8 years) than those in the lower 25% of BMI (49.7 ± 2.8 years). However, they used statistical modeling for calculation of BMI at different ages instead of measuring weight and height at different ages. In a meta-analysis by Tao et al. (24), the positive relationship between BMI and ANM was reported. They noted that most of the included studies had used self-reported BMI rather than measured and calculated values. Moreover, the effect of BMI on ANM was markedly decreased in included studies that were controlled for smoking status. On the other hand, a British cohort of more than 1,000 women has shown no significant association between BMI at different ages and ANM (26). Additionally, a population-based cohort study concluded that BMI was not associated with late stages of menopause while highlighting the effect of BMI on follicular and/or hormonal changes during menopausal transition (16). Butler and Santoro (27) reviewed the possible factors of menopause and ANM and concluded no different ANM in obese and non-obese women.

The exact mechanism by which menopause and ANM affect BMI is not fully understood. Nonetheless, some rationales might explain this: first, menopause strongly correlates with decrease in some hormone levels, such as inhibin B and antimüllerian hormone (AMH). Decreased inhibin B, as seen in ovarian dysfunction and decreased ovarian reserve, is shown to be associated with obesity (28, 29), which is usually seen in menopausal women. In a longitudinal study, obese women had lower AMH levels compared with non-obese ones in late reproductive years (30). Antimüllerian hormone itself reflects ovarian aging and the ANM; it has been shown that AMH is strongly correlated with ANM (31). Our results indicate that women with higher ANM experience a decrease in BMI, which might be due to the relationship between AMH and obesity. Higher ANM is associated with higher levels of AMH, which is inversely correlated to BMI.

Second, because menopause is related to depressive disorders (32), the sooner women experience menopausal transition period, the more psychologically depressed they may become (33). Hence, this may influence their eating behavior and energy intake (34), which are both affected by estrogen levels through central regulation of appetite (35). Results of a longitudinal study showed that both energy intake and expenditure are declined during menopausal transition (36). Menopause and related depressive disorders may also influence physical activity, which can further increase fat mass and alter its distribution (37, 38).

To the best of our knowledge, this is the first population-based cohort study with more than 15 years of short-interval follow-ups that evaluates ANM and its relation to the trend of BMI. We have used a relatively large sample size of participants in a population-based cohort, measured their anthropometric parameters (e.g., WC, BMI) in each follow-up session, and followed them until the end of their reproductive lifespan and menopause. In addition, we used robust statistical methods to analyze the effect of ANM on the trend in obesity. However, our findings are subject to limitations. First, we used self-reported age at natural menopause, which might have suffered from a recall error of a maximum of 3 years (follow-up intervals), although the chance of this error is minimal with repeated questions for ANM at each follow-up. Second, we did not measure other components of obesity, such as fat mass and fat distribution. Nonetheless, most studies did use BMI as a reliable representative index of obesity. Finally, we could not assess the impact of ethnicity on BMI, because our population included just one ethnic group.

To conclude, we have shown that aging and menopause are independently associated with an increase in BMI. These changes are mainly dependent on the age at natural menopause, which has a dual effect on the BMI. In our study, women with lower ANM faced an annual increase of BMI that is proportional to the difference between their ANM and the mean ANM. On the other hand, those with higher ANM experienced an annual decreasing BMI, which is proportionate to the difference of their ANM and the mean ANM.

Acknowledgments: The authors thank each of the study participants for the substantial time and effort contributed to this study; the research staff at the TLGS unit and personnel of the Research Institute for Endocrine Sciences; and Ms. Niloofar Shiva for critical editing of English grammar and syntax of the manuscript.

REFERENCES

1. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. Ageing Res Rev 2009;8:339–48.
2. Guo SS, Zeller C, Chumlea WC, Siervogel RM. Aging, body composition, and lifestyle: the Fels Longitudinal Study. Am J Clin Nutr 1999;70:405–11.
3. World Health Organization. Obesity and overweight. Fact sheet no. 311. Geneva: WHO; 2016.
4. Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, Shah D, et al. Understanding weight gain at menopause. Climacteric 2012;15:419–29.
5. Knowlton AA, Lee AR. Estrogen and the cardiovascular system. Pharmacol Ther 2012;135:54–70.
6. Sutton-Tyrrell K, Zhao X, Santoro N, Lasley B, Sowers M, Johnston J, et al. Reproductive hormones and obesity: 9 years of observation from the Study of Women's Health Across the Nation. Am J Epidemiol 2010;171:1203–13.
7. Matthews KA, Abrams B, Crawford S, Miles T, Neer R, Powell LH, et al. Body mass index in mid-life women: relative influence of menopause, hormone use, and ethnicity. Int J Obes Relat Metab Disord 2001;25:863–73.
8. Sternfeld B, Bhat AK, Wang H, Sharp T, Quesenberry CP Jr. Menopause, physical activity, and body composition/fat distribution in midlife women. Med Sci Sports Exerc 2005;37:1195–202.
9. Pasquali R, Casimirri F, Labate AM, Tortelli O, Pascal G, Anconetani B, et al. Body weight, fat distribution and the menopausal status in women. The VMH Collaborative Group. Int J Obes Relat Metab Disord 1994;18:614–21.
10. Ho SC, Wu S, Chan SG, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. Int J Obes (Lond) 2010;34:1265–74.
11. Pokoradi AJ, Iversen L, Hannaford PC. Factors associated with age of onset and type of menopause in a cohort of UK women. Am J Obstet Gynecol 2011;205:34.e1–13.
12. Stepaniak U, Szafraniec K, Kubinova R, Malyutina S, Peasey A, Pikhart H, et al. Age at natural menopause in three central and eastern European urban populations: the HAPIEE study. Maturitas 2013;75:87–93.
13. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. Int J Epidemiol 2014;43:1542–62.
14. Morris DH, Jones ME, Schoemaker MJ, McFadden E, Ashworth A, Swerdlow AJ. Body mass index, exercise, and other lifestyle factors in relation to age at natural menopause: analyses from the breakthrough generations study. Am J Epidemiol 2012;175:998–1005.
15. Akahoshi M, Soda M, Nakashima E, Tominaga T, Ichimaru S, Seto S, et al. The effects of body mass index on age at menopause. Int J Obes Relat Metab Disord 2002;26:961–8.
16. Sammel MD, Freeman EW, Liu Z, Lin H, Guo W. Factors that influence entry into stages of the menopausal transition. Menopause 2009;16:1218–27.
17. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997;145:124–33.
18. Azizi F, Rahmani M, Emami H, Mirmiran P, Hajipour R, Madjid M, et al. Cardiovascular risk factors in an Iranian urban population: Tehran lipid and glucose study (phase 1). Soz Praventivmed 2002;47:408–26.
19. Azizi F, Khalili D, Aghajani H, Esteghamati A, Hosseinpanah F, Delavari A, et al. Appropriate waist circumference cut-off points among Iranian adults: the first report of the Iranian National Committee of Obesity. Arch Iran Med 2010;13:243–4.
20. Twisk JW. Applied longitudinal data analysis for epidemiology: a practical guide. Cambridge, UK: Cambridge University Press; 2013.
21. Liang KY, Zeger S. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
22. Day FR, Ruth KS, Thompson DJ, Lunetta KL, Pervjakova N, Chasman DI, et al. Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. Nat Genet 2015;47:1294–303.
23. Perry JR, Murray A, Day FR, Ong KK. Molecular insights into the aetiology of female reproductive ageing. Nat Rev Endocrinol 2015;11:725–34.
24. Tao X, Jiang A, Yin L, Li Y, Tao F, Hu H. Body mass index and age at natural menopause: a meta-analysis. Menopause 2015;22:469–74.
25. Trikudanathan S, Pedley A, Massaro JM, Hoffmann U, Seely EW, Murabito JM, et al. Association of female reproductive factors with body composition: the Framingham Heart Study. J Clin Endocrinol Metab 2013;98:236–44.
26. Hardy R, Mishra GD, Kuh D. Body mass index trajectories and age at menopause in a British birth cohort. Maturitas 2008;59:304–14.
27. Butler L, Santoro N. The reproductive endocrinology of the menopausal transition. Steroids 2011;76:627–35.
28. Gracia CR, Freeman EW, Sammel MD, Lin H, Nelson DB. The relationship between obesity and race on inhibin B during the menopause transition. Menopause 2005;12:559–66.
29. Spandorfer SD, Kump L, Goldschlag D, Brodkin T, Davis OK, Rosenwaks Z. Obesity and in vitro fertilization: negative influences on outcome. J Reprod Med 2004;49:973–7.

30. Freeman EW, Gracia CR, Sammel MD, Lin H, Lim LC, Strauss JF 3rd. Association of anti-mullerian hormone levels with obesity in late reproductive-age women. Fertil Steril 2007;87:101–6.
31. Tehrani FR, Solaymani-Dodaran M, Azizi F. A single test of antimullerian hormone in late reproductive-aged women is a good predictor of menopause. Menopause 2009;16:797–802.
32. Freeman EW. Associations of depression with the transition to menopause. Menopause 2010;17:823–7.
33. Harlow BL, Signorello LB. Factors associated with early menopause. Maturitas 2000;35:3–9.
34. Asarian L, Geary N. Sex differences in the physiology of eating. Am J Physiol Regul Integr Comp Physiol 2013;305:R1215–67.
35. Brown LM, Clegg DJ. Central effects of estradiol in the regulation of food intake, body weight, and adiposity. J Steroid Biochem Mol Biol 2010;122:65–73.
36. Duval K, Prud'homme D, Rabasa-Lhoret R, Strychar I, Brochu M, Lavoie JM, et al. Effects of the menopausal transition on dietary intake and appetite: a MONET Group Study. Eur J Clin Nutr 2014;68:271–6.
37. Kanaley JA, Sames C, Swisher L, Swick AG, Ploutz-Snyder LL, Steppan CM, et al. Abdominal fat distribution in pre- and postmenopausal women: the impact of physical activity, age, and menopausal status. Metabolism 2001;50:976–82.
38. Franklin RM, Ploutz-Snyder L, Kanaley JA. Longitudinal changes in abdominal fat distribution with menopause. Metabolism 2009;58:311–5.

Efecto del envejecimiento, la menopausia y la edad de la menopausia natural sobre la tendencia en el índice de masa corporal: una cohorte poblacional de 15 años.

Objetivo: Observar los efectos de la menopausia, la edad de la menopausia natural (EMN) y el envejecimiento sobre la tendencia del índice de masa corporal (IMC).

Diseño: Cohorte prospectiva de 929 mujeres seguidas durante 15 años. Datos obtenidos del Estudio de Lípidos y Glucosa de Teherán.

Marco: No aplica.

Intervención: Ninguna.

Pacientes: De las mujeres participantes en el Estudio de Lípidos y Glucosa de Teherán, se incluyó a 929 que estaban en edad reproductiva en el momento del estudio y menopáusicas en la última sesión de seguimiento. Se midieron datos antropométricos repetidamente cada 3 años y la tendencia en el IMC, asociada a la menopausia y la EMN, se evaluó mediante la ecuación de estimación generalizada.

Medidas de resultados principales: Índice de masa corporal en cada sesión de seguimiento.

Resultados: El modelo ajustado de la ecuación de estimación generalizada ilustra que el IMC aumenta con la edad (ß = 0.16) y el estatus menopáusico (ß = 1.11). También muestra que las mujeres con una EMN más tardía experimentaron un descenso del IMC (ß = -0.03) comparado con las mujeres con una EMN más temprana. El término de interacción de menopausia y tiempo (menopausia x tiempo) tiene un efecto negativo sobre el IMC; esto es, el habitual aumento de IMC tras la menopausia se atenúa con el tiempo (ß = -0.4, intervalo de confianza del 95% -0.6, -0-3).

Conclusiones: La menopausia y el envejecimiento se correlacionan independientemente con el aumento de IMC. La tendencia del IMC, sin embargo, depende de la EMN de las participantes en el estudio: las mujeres con EMN más tardía que la EMN media de nuestra población (i.e., 49 años) se enfrentan a un descenso del IMC comparadas con aquellas con una EMN más temprana.