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Disruptions in ovarian function are related to depression and cardio-metabolic risk during pre-menopause

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Abstract

Objective—To evaluate the extent to which mild disruptions in ovarian function indexed by changes in menstrual cycle length may relate to cardio-metabolic and psychological health in pre-menopausal women.

Methods—Among 804 healthy, regularly-cycling women (ages 25–45, M=35.5 [5.5]), patterns of any change (shortening, lengthening, or increased variability) versus no change in menstrual cycle length were examined in relation to a composite of cardio-metabolic risk and individual risk factors (high-density lipoprotein [HDL], triglycerides, waist circumference, glucose, hypertensive status) as well as in relation to depression indicators (Center for Epidemiologic Studies Depression [CESD] score ≥16 [yes/no], lifetime depression diagnosis [yes/no], lifetime anti-depressant medication use [yes/no]). Models were also explored to test whether changes in menstrual cycle length mediated relations between depression history and cardio-metabolic risk.

Results—In covariate-adjusted models, compared to no change, any change in menstrual cycle length was associated with higher cardio-metabolic risk composite scores and lower HDL (*p's*<.05). In addition, compared to no change, any change in menstrual cycle length was associated with a CESD score ≥16, having received a depression diagnosis, and having used an anti-depressant medication (*p*'s<.05). In exploratory analyses, any change in menstrual cycle length partially mediated the relation between depression history and cardio-metabolic risk (*b*=0.152, *p*=.040) which attenuated (*b*=0.129, *p*=.083) when any change in menstrual cycle length was covaried.

Conclusions—Findings suggest disruptions in ovarian function marked by subtle changes in menstrual cycle length may relate to aspects of cardio-metabolic, and psychological health among healthy, pre-menopausal women.

Keywords

ovarian function; menstrual cycle length; depression; cardiovascular risk; cardio-metabolic risk; metabolic syndrome

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Although risk for cardiovascular disease (CVD) increases during the menopausal transition,[1–12] the disease processes underlying the emergence of CVD during this period may begin pre-menopausally as is suggested by studies documenting fatty streaks as well as clinically significant atherosclerotic lesions in young, pre-menopausal women and adolescent girls.[13–16] To date, however, factors contributing to atherosclerotic disease development pre-menopausally that may explain variability in CVD post-menopausally are poorly understood. In this context, Kaplan and Manuck have proposed the "precocious acceleration" hypothesis, suggesting that disruptions in ovarian function during the pre-menopausal period (even when mild) can promote atherosclerosis, leading to an accelerated course of disease and increased post-menopausal risk for CVD.[17–18] This hypothesis is supported by studies in which women with apparent impairments in ovarian function, marked by anovulation, lower estrogen, and menstrual cycle irregularity, exhibited increased risk for CVD or more problematic CVD risk factor profiles.[19–25]

Poorer psychological health has been associated with disruptions in ovarian function indexed by menstrual cycle characteristics. Findings drawn from three, largely separate literatures show that i) women with psychiatric disorders frequently experience menstrual cycle abnormalities including increased irregularity and patterns of both shorter and longer cycle length[26–29]; ii) psychological stress, especially when extreme, can play an etiological role in the cessation of menses[30–33]; and iii) risk for depressive symptoms increases during peri-menopause, a time when menstrual cycles become less regular due to reproductive aging.[34] Poorer psychological health has also been associated with risk for CVD. In particular, depression, including major and minor depressive disorder as well as depressive symptomatology, has been shown to predict incident myocardial infarction, cardiac-specific, and all-cause mortality.[35–40] With respect to the examination of cardiovascular risk factors, depression, especially among women, confers risk for the development of metabolic syndrome[41–43] and negative psychological factors more broadly are correlated (although not always[41–42]) with the individual components of metabolic syndrome (i.e., high-density lipoprotein [HDL], triglycerides, waist circumference, glucose, and blood pressure).[43–45]

To integrate and extend the existing literature, the primary goal of the current study was to evaluate whether mild disruptions in ovarian function among healthy, regularly-cycling women are related to markers of cardio-metabolic health as well as depression. Given the inter-relations between disruptions in ovarian function, cardio-metabolic risk factors, and depression, secondarily, we also explored a model in which disruptions in ovarian function were proposed to play a mediating role (at least partially) in linking depression and cardio-metabolic risk. The study objectives were pursued in a multi-ethnic sample of 804 healthy, regularly-cycling pre-menopausal women in whom we examined disruptions in ovarian function as marked by having experienced any change (i.e., shortening, lengthening, or becoming more variable) compared to no change in menstrual cycle length in relation to standard cardio-metabolic risk factors and in relation to current depressive symptomatology and depression history.

Methods

Participants

The current sample included participants in the Ovarian Aging (OVA) Study, an investigation of the correlates of reproductive aging. Participants were recruited through Kaiser Permanente (KP) of Northern California, a large, integrated health care delivery system that provides medical care to approximately one third of the population of Northern California. The KP membership compared to the population of Northern California is generally representative in its socio-demographic and health-related characteristics,

especially when the comparison is limited to those with health insurance.[46] Women were included in the OVA Study if they were between 25–45 years of age, had regular menses (i.e., able to predict the start of menses within 5 days), had their uterus and both ovaries intact, self-identified as white, African-American, Latina, Chinese, or Filipina, and were able to speak/read English, Spanish, or Cantonese. Exclusions included the self-report of major medical illnesses, use of medications affecting the menstrual cycle in the 3 months prior to study enrollment, and current pregnancy or breastfeeding.

The OVA Study protocol included an in-person medical history interview, trans-vaginal ultrasound, anthropometric assessment, blood draw, and self-report questionnaires. Of 1019 total participants, 804 women were included in the current analysis. Excluded women (n = 215) were due to the following: 1) menstrual cycle length outside of the 25–35 day range (n = 33); 2) use of a hormonal method of birth control in the past year (n = 25); 3) pattern of change not reflective of shortening, lengthening, or increased variability in menstrual cycle length (n = 127); or 4) missing information on a key variable related to reproductive history, cardio-metabolic health, or reproductive aging (n = 30). In addition, a subset of 553 women with complete questionnaire data were included in analyses examining depression. Questionnaire data were missing for women who were never administered the questionnaires because the questionnaires were not initially included in the study protocol (n = 123) and women who did not return the questionnaires (n = 128). The study protocol was approved by the University of California San Francisco Committee on Human Research as well as the Kaiser Permanente of Northern California Institutional Review Board. Informed, written consent was obtained from all study participants.

Measures

Menstrual cycle characteristics—In an in-person medical history interview, women were asked to report the number of days in their typical menstrual cycle over the past 12 months in categories: 25–27 days, 28–32 days, and 33–35 days. Women were also asked to report whether their typical menstrual cycle in the past 12 months reflected no change in length or had become shorter, longer, or more variable. In the current analyses, change in menstrual cycle length was coded as having experienced any change in menstrual cycle length (i.e., shortening, lengthening, or increased variability) versus having experienced no change in menstrual cycle length.

Cardio-metabolic risk factors—Cardio-metabolic risk factors, including high-density lipoprotein (HDL), triglycerides, waist circumference, glucose, and hypertensive status were assessed. Assays for HDL, triglycerides, and fasting glucose were performed by Quest Diagnostics (San Jose, CA). Lipids were assayed using enzymatic methods and fasting glucose was assayed by the glucose oxidase method. Waist circumference, taken as the average of 2 measurements, was derived from a standardized anthropometric assessment performed by a study nurse. Lastly, previously diagnosed hypertension (yes/no) and use of anti-hypertensive medications (yes/no) were derived from an in-person medical history interview; endorsement of one or both items was used as a surrogate for measured systolic/diastolic blood pressure which was not assessed in the study protocol. A cardio-metabolic risk composite score was derived for use in the current analyses by taking the mean of the standardized values of each of the five individual cardio-metabolic risk factors (with HDL reversed). Computation of a continuously-measured cardio-metabolic risk composite is consistent with several previous investigations.[47–51]

Depressive symptomatology and treatment history—Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CESD).[52–53] The CESD is a 20-item, self-report questionnaire assessing depressive symptoms over the past

week. Each item is scored on a 0–3 point scale. Response choices indicate the frequency with which each symptom (or item) is experienced, ranging from "rarely or none of the time (< 1 day)" scored 0 to "most or all of the time (5–7 days)" scored 3. Following the reversal of scores on 4 positively-worded questions, items are summed to produce a total score (ranging from 0 to 60) with higher values reflecting more depressive symptoms. A total score of ≥16 is a commonly used cut-off due to its correspondence with clinically significant levels of depression.[53–54] The CESD is a well-established instrument with adequate reliability[55–56] and validity.[5356–60] History of depression diagnosis and treatment were assessed using a standardized set of questions asking women to report whether they had ever received a diagnosis of and/or treatment for depression from a medical professional and the type of treatment that was received. Derived from the CESD and depression diagnosis/ treatment history questions, depression variables examined in the current analyses included the CESD total score coded ≥16 (1 = yes, 0 = no), having received a depression diagnosis (1 = yes, 0 = no), and having used an anti-depressant medication (1 = yes, 0 = no). In addition, a lifetime history of depression composite score was computed by coding ever having received a depression diagnosis or used an anti-depressant medication (1 = yes, 0 = no).

Reproductive aging—Reproductive aging was indexed by concentrations of anti-Mullerian hormone (AMH), a biochemical marker of ovarian reserve.[61–62] AMH, secreted by the granulosa cells of the pre-antral and small antral follicles of the human ovary,[63] plays a key regulatory role in folliculogenesis by inhibiting initial recruitment of primordial follicles into the growing pool of follicles.[64–65] Validity for the use of AMH as an indicator of reproductive aging stems from studies showing AMH correlates with the number of primordial follicles[66]; relates inversely to chronological age in adult women[6167]; and predicts menopausal onset[68–69] as well as ovarian response in treatments using assisted reproductive technologies[70–71]. AMH is also stable within and across menstrual cycles[72–76] and is not affected by use of oral contraceptives.[76–77] AMH was assayed using two commercially available ELISAs from Beckman Coulter (Marseille, France) both of which use a two-site sandwich immunoassay. The Immunotech assay was used for the majority of the sample (84%) until this assay was retired and the second generation assay (Gen II) was used for the remainder of the samples. Among 44 women on whom both assays were performed, regression analyses showed excellent correspondence between the assays (R^2 = 0.94) which has also been demonstrated in prior studies.[78–79] AMH values based on the Immunotech assay were adjusted using the equation of the line with Immunotech predicting Gen II. The Gen II assay sensitivity was 0.16 ng/mL, the intra-assay coefficient of variation (CV) was 1.4%, and the inter-assay CV was 12.5%.

Statistical Analyses

Logistic regression analyses were performed to evaluate cardio-metabolic risk as well as depression in relation to the odds of being in one of two groups of women: either having experienced a change in menstrual cycle length (i.e., shortening, lengthening, or increased variability over the past 12 months) or having experienced no change in menstrual cycle length. First, a cardio-metabolic risk composite score (representing 5 individual cardio-metabolic risk factors [HDL, triglycerides, waist circumference, glucose, and hypertensive status] with HDL reversed) was examined in relation to group membership. Secondly, in separate models, 4 indicators of current depressive symptomatology and treatment history (CESD score ≥16 [yes/no], depression diagnosis [yes/no], use of anti-depressant medications [yes/no], lifetime history of depression composite score [yes/no]) were examined in relation to group membership. Next, AMH was added to the models to determine whether associations between cardio-metabolic risk/depression and group membership were independent of variability in reproductive aging. All models included covariate-adjustment for age, race/ethnicity (represented by four dummy coded variables

with white as the referent), socioeconomic status (SES) indexed by individual-level education (1=<HS/some HS; 2=HS grad/GED; 3=some college/AA/vocational school; 4=college graduate; 5=graduate school [PhD, MS]; 6=professional degree [MD, JD, DDS, MBA]), cigarette smoking (1=current/past smoking, 0=never smoked), physical activity level (indexed by MET-hours of moderate/vigorous activity in a typical week over the past 3 months,[80] parity (1=1+ live births, 0=no live births) past use of a hormonal method of birth control (0=no history of use; 1=positive history of use), and menstrual cycle length (1=25–27 days, 2=28–32 days, and 3=33–35 days).

To explore a conceptual model of possible inter-relations between disruptions in ovarian function, cardio-metabolic risk factors, and depression, a series of regression analyses were then performed to evaluate whether change in menstrual cycle length might play a mediational role in linking depression to cardio-metabolic risk. In these analyses, depression was represented by the lifetime history of depression composite score, and cardio-metabolic risk was indexed by the cardio-metabolic risk composite score. In accordance with Baron & Kenny,[81] conditions for testing for mediation were evaluated first by examining relations between 1) the lifetime history of depression composite score and change in menstrual cycle length (Path A); 2) change in menstrual cycle length and the cardio-metabolic risk composite score, controlling for the lifetime history of depression composite score (Path B); and 3) the lifetime history of depression composite score and the cardio-metabolic risk composite score (Path C). In models in which conditions for testing for mediation were met (i.e., Paths A, B, and C were all statistically significant), mediation was then tested by reevaluating Path C with additional covariate-adjustment for change in menstrual cycle length. Attenuation in Path C was interpreted to indicate that change in menstrual cycle length mediates the relation between the lifetime history of depression composite score and the cardio-metabolic risk composite score. Linear regression was performed when continuously measured outcomes were assessed and binary logistic regression was performed when dichotomously coded outcomes were assessed. All models included covariate-adjustment for the same variables defined in detail above (age, race/ethnicity, SES, smoking, physical activity level, parity, past use of a hormonal method of birth control, menstrual cycle length, and AMH).

Results

Sample description

Eighty-one percent (n = 650) of the sample reported experiencing no change in menstrual cycle length while patterns of shortening, lengthening, and increased variability were reported in 7% (n = 57), 5% (n = 38), and 7% (n = 59) of the sample, respectively. In Table 1, descriptive information for the total sample is provided as well as statistical comparisons between women coded: any change in menstrual cycle length (i.e., shortening, lengthening, *or* increased variability) and no change in menstrual cycle length. Women on average were 35.3 (SD=5.5) years old and the sample was ethnically diverse (29.7% white, 24% African-American, 22.9% Latina, 19.3% Chinese, and 4.0% Filipina). Regarding the covariates, women who experienced any change compared to no change in menstrual cycle length were more likely to report past use of a hormonal method of birth control ($p < .01$). Regarding the cardio-metabolic risk variables, women who experienced any change compared to no change in menstrual cycle length had higher cardio-metabolic risk composite scores, lower HDL, and were more likely to have received a hypertensive diagnosis/used anti-hypertensive medication (p's < .05). Lastly, regarding the depression variables, women who experienced any change compared to no change in menstrual cycle length had higher CESD scores (13.7 versus 10.7), were more likely to have a CESD score ≥16 (p's <.01), and were more likely to have received a depression diagnosis or used an anti-depressant medication (p's <.001).

Are disruptions in ovarian function related to cardio-metabolic risk?

As reported in Table 2, results of logistic regression analyses showed that with each 1-unit increase in the cardio-metabolic risk composite score (reflecting the mean of the standardized values of 5 individual cardio-metabolic risk factors [HDL, triglycerides, waist circumference, glucose, hypertensive status] with HDL reversed) the odds of experiencing any change in menstrual cycle length was increased by 43% (OR = 1.429, 95% CI = 1.063–1.920) compared to experiencing no change in menstrual cycle length. In addition, with each 1 SD increase in HDL the odds of experiencing any change in menstrual cycle length was decreased by 24% (OR = 0.765, 95% CI = 0.628–0.933) compared to experiencing no change in menstrual cycle length. Greater waist circumference and hypertensive status were also associated with an increased odds of experiencing any change compared to no change in menstrual cycle length albeit at the level of a statistical trend (p's <.10). Triglycerides and glucose were unrelated to categories of any change compared to no change in menstrual cycle length (p's >.05). All results included adjustment for covariates, including age, race/ethnicity, SES, cigarette smoking, physical activity level, parity, past use of a hormonal method of birth control, and menstrual cycle length. When analyses were repeated with additional covariate-adjustment for AMH, the pattern of results did not change (results not shown), suggesting associations between cardio-metabolic risk and change in menstrual cycle length were not attributable to variability in reproductive aging.

Are disruptions in ovarian function related to depression?

As reported in Table 3, results of logistic regression analyses showed that having a CESD score ≥16, having received a depression diagnosis, and having used an anti-depressant medication were associated with a 2.1, 3.0, and 3.1 increased odds, respectively, of experiencing any change compared to no change in menstrual cycle length. Examination of the lifetime history of depression composite score, reflecting endorsement of having received a depression diagnosis *or* having used an anti-depressant medication [1 = yes, 0 = no] was associated with a 2.6 increased odds of experiencing any change compared to no change in menstrual cycle length. All results included adjustment for covariates, including age, race/ethnicity, SES, cigarette smoking, physical activity level, parity, past use of a hormonal method of birth control, and menstrual cycle length. When analyses were repeated with additional covariate-adjustment for AMH the pattern of results did not change (results not shown) suggesting associations between indicators of depressive symptomatology/treatment history and change in menstrual cycle length were not attributable to variability in reproductive aging.

Does ovarian function play a mediating role in linking depression to cardio-metabolic risk?

As reported in Table 4, in covariate-adjusted analyses (controlling for age, race/ethnicity, SES, cigarette smoking, physical activity level, parity, past use of a hormonal method of birth control, menstrual cycle length, and AMH), conditions for testing for mediation were met. That is, regarding Path A, the lifetime history of depression composite score was related significantly to change in menstrual cycle length (b = 0.990, p = .001, OR = 2.692, 95% CI = 1.507–4.808). Regarding Path B, change in menstrual cycle length was related significantly to the cardio-metabolic risk composite score (b = 0.125, p = .040), adjusted for the lifetime history of depression composite score. Regarding Path C, the lifetime history of depression composite score was related significantly to the cardio-metabolic risk composite score (b = 0.152, p = .040). When Path C was re-evaluated including additional covariate-adjustment for change in menstrual cycle length, the association between the depression composite score and the cardio-metabolic risk composite score attenuated (b = 0.129, p = .083), suggesting change in menstrual cycle length partially mediates the relation between the lifetime history of depression composite score and the cardio-metabolic risk composite score (see Figure 1).

Discussion

In cross-sectional analyses of 804 healthy, regularly-cycling pre-menopausal women, results indicated that any change in menstrual cycle length in the previous 12 months versus no change was associated with increased cardio-metabolic risk and depression. Associations were independent of statistical control for age, race/ethnicity, SES, cigarette smoking, physical activity level, parity, past use of a hormonal method of birth control, and menstrual cycle length. When AMH, a marker of ovarian reserve, was additionally covaried results did not change, suggesting variability in reproductive aging at least in this relatively young (mean age of 35) pre-menopausal sample of women does not account for associations between changes in menstrual cycle length and cardio-metabolic risk/depression. Lastly, results of exploratory analyses (albeit based on cross-sectional data) supported the proposed conceptual model suggesting that ovarian function may play a mechanistic role in linking depression to cardio-metabolic risk as demonstrated by results in which any change compared to no change in menstrual cycle length partially mediated the relation between lifetime history of depression and the cardio-metabolic risk composite score.

Each one-unit increase in the cardio-metabolic risk composite score (reflecting the composite of five individual cardio-metabolic risk factors, including HDL [reversed], triglycerides, waist circumference, glucose, and hypertensive status) was associated with a 43% increased odds of experiencing any change compared to no change in menstrual cycle length. This finding is consistent with prior studies in which menstrual cycle irregularity has been shown to be an independent risk factor for CVD.[21–2325] However, irregularity has been defined inconsistently and commonly represents more extreme patterns (e.g., very short [<21 days] or very long [≥40 days] cycles) that may reflect an underlying clinical condition such as polycystic ovarian syndrome. Other prior studies have also reported a longer menstrual cycle length was associated with CVD risk factors, including higher BMI and lower HDL[1982–83] although menstrual cycle length and not *change* in menstrual cycle length was examined in these studies. Thus, the current findings are unique in suggesting more subtle changes in menstrual cycle length among healthy, regularly-cycling women are also related to cardio-metabolic risk and that *change* in menstrual cycle length even independently of menstrual cycle length itself may contribute to this risk.

Indicators of depressive symptomatology and treatment history were associated with experiencing any change compared to no change in menstrual cycle length. Associations were present across a range of depression indicators representing normative variability in depressive symptoms as well as more clinically significant outcomes. In particular, the lifetime history of depression composite score, reflecting having ever received a depression diagnosis or having ever used an anti-depressant medication, was associated with a 2.6-fold increase in the odds of experiencing any change compared to no change in menstrual cycle length. Our findings are generally consistent with previous studies showing women with psychiatric disorders disproportionately experience abnormalities in menstrual cycle characteristics reflected by irregular cycles as well as patterns of both shorter and longer length.[26–29] However, as mentioned previously with respect to the examination of cardio-metabolic risk, menstrual cycle length and not *change* in menstrual cycle length was examined in these studies.

All models were re-evaluated additionally including AMH as a covariate to account for the possibility that self-reported changes in menstrual cycle length may reflect accelerated reproductive aging which has itself been recently linked to depressive symptomatology and psychological stress.[84–85] In descriptive analyses, mean levels of AMH were lower among women reporting any change compared to no change in menstrual cycle length which is consistent with studies suggesting menstrual cycles initially shorten with age.[86–87] However,

the inclusion of AMH in multivariate models did not account for associations between any change compared to no change in menstrual cycle length and cardio-metabolic risk/depression, indicating that reproductive aging did not make a significant contribution to the current model. It remains possible, however, that as the current sample ages and the number of women experiencing changes in menstrual cycle length increases, variability in reproductive aging may become a more prominent factor in explaining these changes.

The current study had several significant weaknesses, including that patterns of change in menstrual cycle length were self-reported and retrospective with women reporting changes in a typical cycle over the past 12 months. Also, depression indicators, having received a depression diagnosis and use of an anti-depressant medication, were derived from a self-report questionnaire and were not confirmed by other sources such as a diagnostic psychiatric interview or medical records. In addition, because of the small number of women in each change category (i.e., shortening, lengthening, or increased variability) we could not analyze these groups separately. Most notably, because the analyses were cross-sectional, the direction of association between the variables of interest cannot be determined. In particular, while we proposed on an exploratory basis a conceptual model suggesting that depression may negatively impact ovarian function as well as cardio-metabolic risk (possibly via disruptions in ovarian function), it is plausible that associations are actually bi-directional. That is, depressive symptomatology may also result from disruptions in ovarian function and cardio-metabolic risk factors may play a role in promoting depressive symptoms.[88–89] A primary strength of the current study was its novel emphasis on examining disruptions in ovarian function among women who are healthy and regularly-cycling. In addition, the sample itself was well-characterized in terms of reproductive history, cardio-metabolic risk factors, and potential confounding variables.

Conclusions

On the whole, results provide indirect support for Kaplan and Manuck's "precocious acceleration" hypothesis which proposes that even mild disruptions in ovarian function pre-menopausally may promote atherosclerosis.[17–18] In summary, findings from the current study suggest that subtle disruptions in ovarian function marked by changes in menstrual cycle length are observable even in healthy, regularly cycling women and these changes (compared to no change) are associated with increased cardio-metabolic risk and depression. In addition, exploratory analyses suggest changes in menstrual cycle length may partially mediate relations between depression and cardio-metabolic risk although this finding should be considered preliminary only due to the cross-sectional nature of the data. Future longitudinal studies are needed to more fully examine the complex inter-relations between reproductive, cardio-metabolic, and psychological health in women and to delineate the mechanisms linking these areas.

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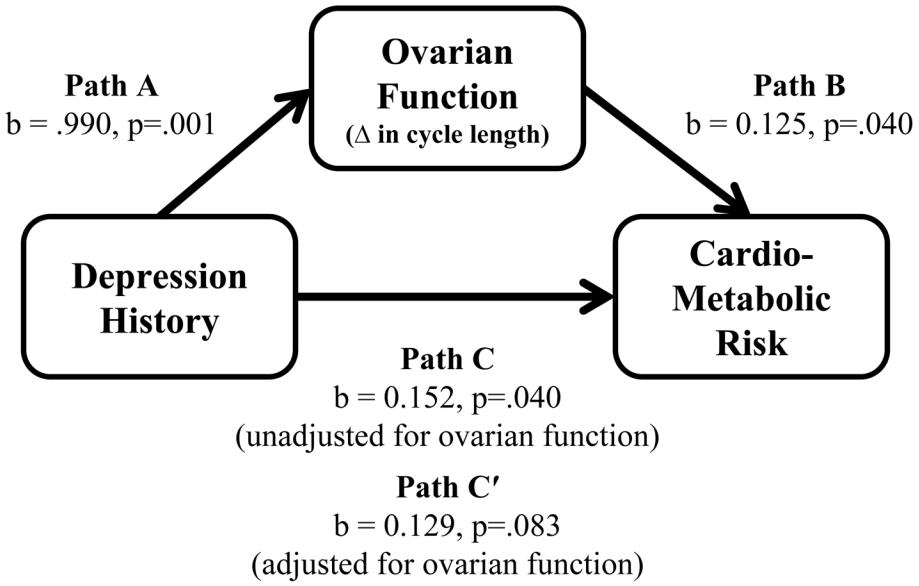

Figure 1.

Mediational model depicting the attenuation in the association between depression history and cardio-metabolic risk following adjustment for ovarian function.*

* Depression history was represented by the lifetime history of depression composite score coded having received a depression diagnosis or having used anti-depressant medications (1 = yes, 0 = no); ovarian function was indexed by change in menstrual cycle length coded any change (shorter, longer, or more variable) vs. no change; cardio-metabolic risk was represented by the cardio-metabolic risk composite score reflecting the mean of standardized values of 5 individual risk factors (HDL, triglycerides, waist circumference, glucose, hypertensive status).

Table 1

Comparison of women experiencing any change compared to no change in menstrual cycle length.

	Total (n = 804) Mean (SD) or %	Any change (n = 154) Mean (SD) or %	No change (n = 650) Mean (SD) or %	Test Statistic	p
Covariates:					
Age	35.3 (5.5)	36.0 (5.7)	35.2 (5.4)	$t = -1.52$	.129
White	29.7%	34.4%	28.6%	$\chi^2 = 2.01$	.157
AA	24.0%	28.6%	22.9%	$\chi^2 = 2.18$	.140
Latina	22.9%	18.2%	24.0%	$\chi^2 = 2.39$	.122
Chinese	19.3%	14.3%	20.5%	$\chi^2 = 3.05$	.081
Filipina	4.0%	4.5%	3.8%	$\chi^2 = 0.16$	.690
Education[g]	3.5 (1.3)	3.6 (1.2)	3.5 (1.3)	$t = -0.97$	.802
Smoking (% current/past)	23.9%	25.3%	23.5%	$\chi^2 = 0.22$	.640
Physical activity level (MET-hours)	8.8 (10.3)	8.4 (9.1)	8.9 (10.6)	$t = 0.48$	.629
Parity (1=1+live births, 0=no live births)	44.7%	47.4%	44.0%	$\chi^2 = 0.58$	.445
Birth control (% past use)	69.2%	77.9%	67.1%	$\chi^2 = 6.87$	.009
Cardio-metabolic factors:					
Cardio-metabolic composite	0.0 (0.6)	0.10 (0.6)	−0.02 (0.6)	$t = -2.26$	.024
HDL	59.6 (15.8)	57.1 (14.7)	60.2 (15.9)	$t = 2.19$	.029
Triglycerides	90.7 (60.5)	93.1 (62.8)	90.2 (59.9)	$t = -0.54$	.588
Waist Circumference	84.9 (15.5)	86.7 (16.9)	84.5 (15.1)	$t = -1.61$	.107
Glucose	87.3 (9.7)	87.8 (9.1)	87.2 (9.9)	$t = -0.62$	.535
Hypertension (% w dx)	8.1%	12.3%	7.1%	$\chi^2 = 4.64$	.031
Reproductive Aging:					
AMH (ng/mL)	3.1 (2.8)	2.7 (2.6)	3.2 (2.8)	$t = 1.91$	.056
	(*n* = 553)	**(*n* = 107)**	**(*n* = 446)**		
Depression:					
CESD score	11.3 (8.3)	13.7 (9.8)	10.7 (7.8)	$t = -3.39$	.001
CESD 16+, (1=yes, 0=no)	27.1%	37.4%	24.7%	$\chi^2 = 7.06$	.008
Lifetime depression dx, (1=yes, 0=no)	8.7%	18.5%	6.5%	$\chi^2 = 15.78$	<.001
Lifetime antidepressant use, (1=yes, 0=no)	8.5%	18.5%	6.5%	$\chi^2 = 15.78$	<.001

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	Total (n = 804)	Any change (n = 154)	No change (n = 650)	Test Statistic	p
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %		
Lifetime depression composite	12.5%	24.1%	10.0%	$\chi^2 = 15.46$	<.001

[g]Education was coded 1=<HS/some HS; 2=HS grad/GED; 3=some college/AA/vocational school; 4=college graduate; 5=graduate school (PhD, MS); 6=professional degree (MD, JD, DDS, MBA).

Table 2

Results reported from the final models of separate logistic regression analyses examining cardio-metabolic risk in relation to experiencing any change compared to no change in menstrual cycle length.[a]

	Any change in menstrual cycle length (n = 154) vs. No change (n = 650)		
	OR	**95% CI**	**p**
Cardio-metabolic risk composite	1.429	1.063 – 1.920	.018
HDL	0.765	0.628 – 0.933	.008
Triglycerides	1.062	0.894 – 1.262	.495
Waist circumference	1.209	0.984 – 1.484	.071
Glucose	1.032	0.864 – 1.232	.729
Hypertension dx (1=yes, 0=no)	1.727	0.950 – 3.139	.073

[a]Analyses included covariate-adjustment for age, race/ethnicity, SES, smoking, physical activity level, parity, past use of a hormonal method of birth control, and menstrual cycle length; individual cardio-metabolic risk factors (HDL, triglycerides, waist circumference, and glucose) were standardized prior to entry into the regression models.

Table 3

Results reported from the final models of separate logistic regression analyses examining indicators of depressive symptomatology and psychiatric treatment history in relation to experiencing any change compared to no change in menstrual cycle length.[a]

	Any change in menstrual cycle length (n = 154) vs. No change (n = 650)		
	OR	**95% CI**	**p**
CESD score ≥16, (1=yes, 0=no)	2.052	1.280 – 3.290	.003
Lifetime depression dx, (1=yes, 0=no)	2.986	1.569 – 5.682	.001
Lifetime antidepressant use, (1=yes, 0=no)	3.061	1.576 – 5.946	.001
Lifetime depression composite, (1=yes, 0=no)[b]	2.615	1.469 – 4.657	.001

[a] Analyses included covariate-adjustment for age, race/ethnicity, SES, smoking, physical activity level, parity, past use of a hormonal method of birth control, and menstrual cycle length

[b] The lifetime history of depression composite score is coded having received a depression diagnosis or having used anti-depressant medications (yes/no).

Table 4

Results reported from the final models of separate regression equations examining paths in the proposed meditational model to determine whether ovarian function indexed by change in menstrual cycle length mediates the relation between depression history and cardio-metabolic risk.[a]

Path A		Path B		Path C		Path C′	
Depression[b] → Ovarian Fx[c]		Ovarian Fx[c] → Cardio-metabolic Risk[d]		Depression[b] → Cardio-metabolic Risk[d] (unadjusted for ovarian function)		Depression[b] → Cardio-metabolic Risk[d] (adjusted for ovarian function)	
b	p	b	p	b	p	b	p
.990	.001	0.125	.040	0.152	.040	0.129	.083

[a]Analyses included covariate-adjustment for age, race/ethnicity, SES, smoking, physical activity level, parity, past use of hormone-containing medication for birth control, menstrual cycle length, and AMH.

[b]Depression was represented by the lifetime history of depression composite score coded having received a depression diagnosis or having used anti-depressant medications (yes/no).

[c]Ovarian function was indexed by change in menstrual cycle length coded any change vs. no change.

[d]Cardio-metabolic risk was represented by the cardio-metabolic risk composite score reflecting the mean of standardized values of 5 individual risk factors (HDL, triglycerides, waist circumference, glucose, hypertensive status) with HDL reversed.