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Age at menarche and depressive symptoms in older Southern Chinese women: a Mendelian randomization study in the Guangzhou Biobank Cohort Study

Shiu Lun Au Yeung[a], Chaoqiang Jiang[b], Kar Keung Cheng[c], Lin Xu[a], Weisen Zhang[b], Tai Hing Lam[a,b*1], Gabriel Matthew Leung[a], C Mary Schooling[a,d]

[a]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[b]Guangzhou Number 12 Hospital, Guangzhou, China

[c]Department of Public Health and Epidemiology, University of Birmingham, UK

[d] City University of New York, Graduate School of Public Health and Health Policy, New York, NY, USA

hrmrlth@hku.hk

Abstract

To clarify the causal role of age at menarche in depressive symptoms we conducted a Mendelian randomization study using a large Southern Chinese cohort (*n*=12,233). A genetic allele score was derived using stepwise regression with cross validation. Older age at menarche was not associated with geriatric depression scale score. Our findings suggest that higher rates of depression in women are likely attributable to other factors which require investigation.

Abbreviations
DNA: Deoxyribonucleic acid; GBCS: Guangzhou Biobank Cohort Study; GDS: Geriatric Depression Scale; GWAS: Genome wide association study; RCTs: Randomized controlled trials; SEP: Socioeconomic position; SNP: Single nucleotide polymorphism

[1] School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, G/F, Patrick Manson Building, 7 Sassoon Road, Hong Kong SAR,China, Phone: (852) 3917 9287

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1. Introduction

Women have higher risk of depression than men (Riecher-Rossler, 2017), possibly due to differences in social roles and norms, vulnerability to adverse life events, or estrogen (Kuehner, 2017; Piccinelli and Wilkinson, 2000). Observations concerning the relation of age at menarche, a proxy for estrogen exposure (on the basis of similar associations with breast and endometrial cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Day et al., 2017; Rossouw et al., 2002)), with depression are mixed (Herva et al., 2004; Joinson et al., 2013; Wang et al., 2016). These discrepancies may be due to short-term effects, contextually specific effects, or confounding by childhood adiposity and lower socioeconomic position (SEP). Specifically, obesity increases leptin whereas lower SEP may provide cues for inducing earlier initiation of reproduction, all of which may lead to earlier age at menarche (Al-Sahab et al., 2010; Villamor and Jansen, 2016). Randomized controlled trials (RCTs) of age at menarche are impossible. Trials of one mediating pathway, i.e., estrogen, are inconclusive (Demetrio et al., 2011; Gleason et al., 2015). To address this question, Mendelian randomization offers a way forward as this design uses genetic variants associated with age at menarche randomly allocated at conception and hence is less susceptible to confounding by childhood adiposity or SEP (Lawlor et al., 2008). The most recent Mendelian randomization study only addressed the effect of age at menarche on depressive symptoms in adolescence (Sequeira et al., 2017), uncertainty exists as to whether age at menarche has long-term effects on adult depression. To clarify we conducted a Mendelian randomization study of age at menarche on depressive symptoms among older Chinese women.

Given later age at menarche is associated with taller height (Onland-Moret et al., 2005), we considered height as a positive control outcome (Lipsitch et al., 2010).

2. Methods

The Guangzhou Biobank Cohort Study (GBCS) is an ongoing collaboration of Guangzhou Number 12 Hospital, the Universities of Hong Kong and Birmingham, UK, which has been described in detail elsewhere (Jiang et al., 2006). Age at menarche was recorded in years (as per the Gregorian calendar and related interpretation of age), rounded to the nearest year (e.g., 13 years represents the onset of menarche from 12 years 6 months to 13 years 5 months) (Heys et al., 2007). Depressive symptoms were assessed by the Chinese version of the 15-item Geriatric Depression Scale (GDS) which has been used before in Chinese (Lin et al., 2014).

The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved GBCS, including the use of genetic data. All participants gave written, informed consent prior to participation.

2.1 Deoxyribonucleic acid (DNA) extraction and single nucleotide polymorphism (SNP) analysis

DNA was extracted at Guangzhou Number 12 Hospital from buffy coat previously stored at -80°C using a magnetic bead extraction procedure (MagPure Blood DNA Mini Kit). DNA concentrations were checked by Nanodrop (Thermoscientific, USA). For DNA concentrations <15 ng/µl, a silica-based column method was also used to re-extract DNA manually (HiPure

Blood DNA Mini Kit). Almost all (92%) of the DNA samples passed quality control before genotyping. Genotyping was performed using the MassARRAY Sequenom platform (San Diego, CA, USA) at the Beijing Genomics Institute, Beijing. The average genotyping call rate of these SNPs was 98%.

2.2 Genetic Instruments

A priori, we selected 12 SNPs previously reported strongly associated with age at menarche which vary in East Asian populations, including rs13357391, rs1859345, rs2348186 and rs7701979 (*SPOCK)*, rs17268785 (*CCDC85A*), rs2090409, rs4452860, rs7861820 (9q31.2 region) and rs314276, rs369065, rs4946651, rs7759938 (*LIN28B*) (Dvornyk and Waqar-ul-Haq, 2012), because no genome wide association study (GWAS) of age at menarche in East Asians was available when we conducted the study. Correlations between SNPs are from SNP Annotation and Proxy Search (http://www.broad.mit.edu/mpg/snap/ldsearchpw.php) using the HapMap (release #22, JPT+CHB) reference. For SNPs in linkage disequilibrium ($r^2 \geq 0.8$), the SNP with a larger p-value was discarded. rs13357391 and rs7701979 were discarded because of correlation with rs1859345 and rs7759938 because of correlation with rs4946651. The remaining 9 SNPs were considered for inclusion in a genetic allele score to reduce the likelihood of weak instrument bias (Lawlor et al., 2008). The same approach has been used in our previous study (Au Yeung et al., 2017).

The outcome was GDS score for depressive symptoms.

2.3 Statistical analysis

We tested Hardy-Weinberg equilibrium at the SNP locus on a contingency table of observed-versus-predicted frequencies with an exact test. SNPs which deviated from equilibrium were discarded. We used stepwise linear regression to find a parsimonious set of SNPs which predicted age at menarche, with significance set at 0.20, as previously (Zhao et al., 2014). To reduce the likelihood of false positive in the selection of SNPs based on one sample, we used 10-fold cross validation (k=10) (Schonlau, 2005). The F-statistic for age at menarche on genetic score was obtained, a value ≥10 indicates weak instrument bias is unlikely (Lawlor et al., 2008). We used analysis of variance to assess whether genetically estimated age at menarche was associated with potential confounders. We conducted instrumental variable analysis using 2 stage least squares, with the genetic score as the instrument, to assess the associations of age at menarche with GDS score and height. For comparison, we also present estimates from multivariable linear regression, adjusting for education, and recruitment phase (model 1) and additionally adjusting for age, smoking, alcohol use, physical activity, and job type (model 2).

All statistical analyses were conducted using Stata 13.1 (StataCorp LP, College Station, Texas, USA).

3. Results

Among 22,054 women in GBCS, 12,679 had at least one SNP after excluding correlated SNPs. rs369065 and rs2348186 deviated from Hardy Weinberg equilibrium (p=0.04 and p<0.001

respectively) and were discarded. rs314276 was discarded as only 8,068 women (63%) had this SNP. From the stepwise regression with cross validation, rs17268785 (*CCDC85A*), rs1859345 (*SPOCK*), rs2090409 (9q31.2 region), rs4452860 (9q31.2 region) and rs4946651 (*LIN28B*) predicted age at menarche with a p value of ≤ 0.20 in at least 5 of the datasets and were used in the genetic allele score (F-statistic 19.9, n=12,290). The mean age at menarche in this cohort was 14.95 years with standard deviation 2.0.

Genetically estimated age at menarche was not associated with age, smoking, physical activity, education, or job type, but was associated with alcohol use, with a very small difference, as shown in our previous study (Au Yeung et al., 2017). Observationally older age at menarche was associated with higher GDS score (Table 1) in model 1 but not in model 2. Using Mendelian randomization, older age at menarche was not clearly associated with GDS score, but was associated with taller height. Repeating the analyses without rs2090409 and rs4452860, which did not replicate well in the cross validation, showed directionally similar results although estimates had wider confidence intervals. Repeating the analysis excluding the samples with re-extraction (10%) did not change the conclusion from the Mendelian randomization analysis (data not shown).

4. Discussion

This Mendelian randomization study showed that age at menarche was not clearly associated with depressive symptoms although we cannot rule out such an association. Consistent with these findings, estrogen is not clearly associated with depressive symptoms in RCTs (Demetrio

et al., 2011; Gleason et al., 2015), or Mendelian randomization study (Au Yeung et al., 2016). As such, other means to reduce the gender inequalities in mental health are required.

We used Mendelian randomization in a large sample, but limitations exist. First, Mendelian randomization studies have stringent assumptions. The SNPs were selected *a priori* from a previous GWAS of age at menarche, and are related to other phenotypes, such as diabetes (*CCDC85A*), proteoglycan (*SPOCL*) and cancer (9q31.2 and *LIN28B*) but these conditions are not known to be directly associated with depressive symptoms. In addition, we could not include all SNPs from previous GWAS (Perry et al., 2014). Second, age at menarche was based on recall although high correlations between recalled and actual age at menarche have been found (Must et al., 2002). Third, Mendelian randomization studies can be underpowered although our study showed the expected relation with height. Finally, not all SNPs were available for all GBCS participants. However, our estimates would only be biased if genotype determined follow up, which was unlikely.

Our study does not provide strong evidence that age at menarche, possibly an indication of estrogen exposure, contributes to higher rates of depression in women. The difference is likely to be attributable to other factors, such as structural gender inequities, which require investigation in further studies.

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Conflict of interest

Dr Au Yeung reports no disclosures.

Dr Jiang reports no disclosures.

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Table 1: Association of age at menarche (years) with Geriatric Depression Scale (GDS) score in 12,233 Southern Chinese older women in the Guangzhou Biobank Cohort Study using Mendelian randomization and multivariable regression analysis

	Mendelian randomization						[a,b]Multivariable linear regression					
	All SNPs (*F*-statistics: 19.9)			Excluding rs2090409 and rs4452860 (*F*-statistics: 16.9)			Model 1			Model 2		
	n	*β*	*95% CI*	*n*	*β*	*95% CI*	*n*	*β*	*95% CI*	*n*	*β*	*95% CI*
GDS	12,233	-0.43	-0.93 to 0.06	12,362	-0.43	-0.96 to 0.09	12,643	0.023	0.004 to 0.04	12,484	0.017	-0.002 to 0.04
Height (cm)	12,279	1.36	0.038 to 2.69	12,410	1.39	-0.03 to 2.82	12,692	0.13	0.08 to 0.17	12,533	0.19	0.14 to 0.24

[a]Model 1 adjusted for education and recruitment phase; Model 2 additionally adjusted for age, smoking, alcohol use, physical activity, and job type

Highlights

- Mendelian randomization (MR) study is more resistant to confounding.
- This MR study showed menarche unrelated to depressive symptoms.
- Larger MR studies would be necessary to verify our findings.