Human Reproduction, pp. 1–9, 2020
doi:10.1093/humrep/dez259

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Age at natural menopause and development of chronic conditions and multimorbidity: results from an Australian prospective cohort

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Submitted on June 4, 2019; resubmitted on November 12, 2019; editorial decision on November 14, 2019

STUDY QUESTION: Is age at natural menopause (ANM) associated with the development of multiple chronic conditions (multimorbidity) in postmenopausal life?

SUMMARY ANSWER: Women with premature menopause experience increased odds of developing individual chronic conditions and multimorbidity.

WHAT IS KNOWN ALREADY: ANM is considered as a marker of age-related morbidity and mortality in postmenopausal life. Multimorbidity affects more than 60% of older women and has been recognized as the most common 'chronic condition'. Few studies have examined the association between ANM and the development of multimorbidity.

STUDY DESIGN, SIZE, DURATION: A prospective national cohort study of 11 258 Australian women, aged 45–50 years in 1996. Women were followed from 1996 to 2016.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Information about ANM and 11 chronic conditions (diabetes, hypertension, heart disease, stroke, arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, depression, anxiety and breast cancer) were estimated approximately every 3 years. Multimorbidity is defined as 2 or more of these 11 conditions. Generalized estimating equations were used to link the categorical ANM with individual chronic conditions and multimorbidity.

MAIN RESULTS AND THE ROLE OF CHANCE: Among 5107 women reporting ANM, 2.3% experienced premature menopause (≤40 years) and 55.1% developed multimorbidity. Compared with women who experienced menopause at age 50–51 years, women with premature menopause had twice the odds of experiencing multimorbidity by age 60 (OR = 1.98, 95% CI 1.31 to 2.98) and three times the odds of developing multimorbidity in their 60s (OR = 3.03, 95% CI 1.62 to 5.64). Women with premature menopause also experienced higher incidence of most individual chronic conditions.

LIMITATIONS, REASONS FOR CAUTION: The main limitation of this study was the use of self-reported data, but with repeated assessments from prospective study design and the validity of most of the chronic conditions from hospital data, the potential for non-differential misclassification is minimized.

WIDE IMPLICATIONS OF THE FINDINGS: To our knowledge, this is the first study to assess the association of premature menopause and development of multimorbidity in a larger national cohort of mid-aged women. Health professionals should consider comprehensive screening and assessment of risk factors for multimorbidity when treating women who experienced premature menopause.

STUDY FUNDING/COMPETING INTEREST(S): The Australian Longitudinal Study on Women's Health was supported by the Australian Government Department of Health. X.X. is funded by an International Postgraduate Research Scholarship from the Australian government and a UQ Centennial Scholarship from The University of Queensland. G.D.M. is supported by the National Health and Medical Research Council Principal Research Fellowship (APP1121844). None of the authors has any conflicts of interest to declare.

Key words: chronic diseases / multimorbidity / age at natural menopause / premature menopause / cohort study

Introduction

As life expectancy is more than 80 years for women in high-income countries, a third of a woman's life is spent after menopause. The post-menopausal status coincides with increased risks for a range of chronic conditions (Gartlehner *et al*., 2017). The timing of final menstrual period (age at menopause) differs largely in women and is considered as a marker of age-related morbidity and mortality in postmenopausal life (Jaspers *et al*., 2015; Mishra *et al*., 2017). For instance, empirical evidence has uncovered the associations between a woman's age at menopause and her subsequent risk of cardiovascular disease (de Kat *et al*., 2017), diabetes (Pandeya *et al*., 2018, Slopien *et al*., 2018), chronic lung diseases (Campbell *et al*., 2018; Matulonga-Diakiese *et al*., 2018), osteoporosis, cognitive function and dementia (Ryan *et al*., 2014; Georgakis *et al*., 2016), mental disorders (de Kruif *et al*., 2016) and premature death (Ossewaarde *et al*., 2005). However, few studies have examined the association between age at menopause and the development of multiple chronic conditions (also known as multimorbidity).

Loss of ovarian hormones (primarily estrogen) due to menopause affects multiple organs and systems, which further leads to multimorbidity (van Dijk *et al*., 2015; Rocca *et al*., 2018). Multimorbidity affects more than 60% of elderly women and has been recognized as the most common 'chronic condition' in older persons (Tinetti *et al*., 2012; Xu *et al*., 2017). Multimorbidity is now an emerging research and practice focus for women's postmenopausal health (van Dijk *et al*., 2015). For instance, Rocca and colleagues found that women who underwent oophorectomy before age of 46 years (premature or early surgical menopause) also experienced an increased risk of accumulation of multimorbidity (number of 18 chronic conditions) compared to women who experienced natural menopause (hazard ratio = 1.22; 95% CI, 1.14–1.31) (Rocca *et al*., 2016; Rocca *et al*., 2017). However, there is a paucity of prospective data on the association between age at menopause and the development of multimorbidity among women with natural menopause.

Understanding age at natural menopause (ANM) in relation to the development of chronic conditions and multimorbidity could lead to new strategies to prevent and manage these chronic conditions and multimorbidity (Lobo *et al*., 2014; van Dijk *et al*., 2015). In this article, we used data from a prospective cohort of mid-aged women over 20 years to determine whether ANM is associated with the development of individual chronic conditions and multimorbidity.

Materials and Methods

Ethical approval

The study has current ethical approval from Human Research Ethics Committees at the Universities of Newcastle (Newcastle, NSW) and Queensland (Brisbane, QLD).

Study populations

We used data from the Australian Longitudinal Study on Women's Health (ALSWH), which is an ongoing population-based cohort study of factors affecting the health and well-being of Australian women. Women were randomly selected from the national Medicare Australia database, which covers all Australian citizens and permanent residents, including refugees and immigrants. Recruitment methods and response rates have been described in detail elsewhere (Lee *et al*., 2005; Dobson *et al*., 2015). There are three cohorts of women born in 1973–1978, 1946–1951 and 1921–1926 in the ALSWH.

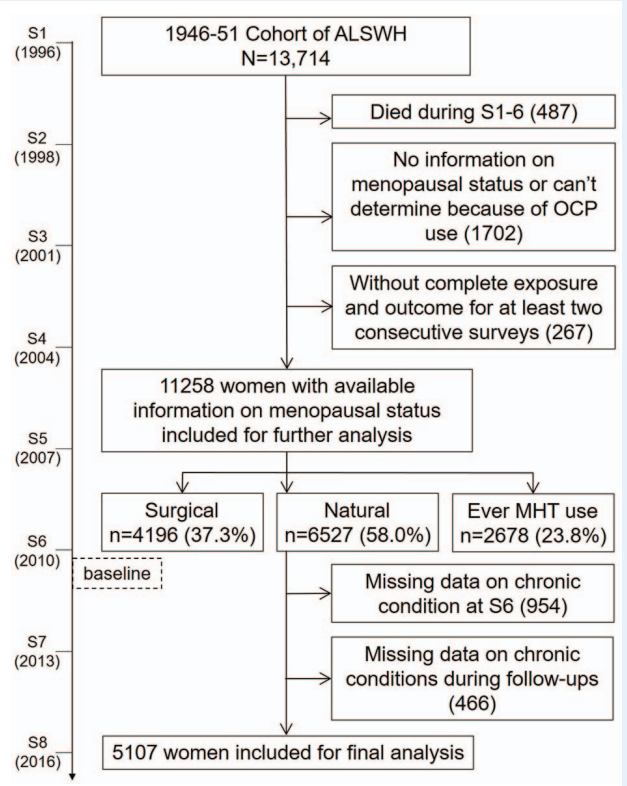

Figure 1 Diagram of the study design and selection of participants.

Data from the 1946–1951 cohort was used for the current study. A total of 13 714 women aged 45–50 years responded to the first survey (S1) in 1996, then followed up with self-administered questionnaires every 3 years (apart from a 2-year interval between the first and second surveys) until 2016. Response rates to the first mailed survey (baseline) cannot be exactly specified, as some women selected for the sample may not have received the invitation (e.g. if they had died or had changed their address without notifying the Health Insurance Commission). It is estimated that 53–56% responded to the initial invitation to participate. Nearly all women reported their natural menopausal status as 'post-menopause' by the sixth wave of the survey (S6; ages 59–64, 2010), and this survey was used as baseline survey for the current study. We excluded women with missing information on menopausal status or with chronic conditions or those who did not participate in at least two consecutive surveys with relevant information on exposures and outcomes of interest (see Fig. 1).

Main outcome and exposure variables

Chronic conditions and multimorbidity

The outcome of interest was a list of 11 chronic conditions: diabetes, hypertension, heart disease, stroke, arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, depression, anxiety and breast cancer. These highly prevalent conditions have been identified as the

National Health Priority Areas in Australia (Australian Institute of Health and Welfare, 1997).

Women were asked if they had been diagnosed with or treated for each condition in the past 3 years, to which they could respond 'yes' or 'no'. We defined the incidence of a condition as the first survey at which it was reported after 2010. Previous studies have validated many included chronic conditions (i.e. diabetes, cancer, heart disease, stroke, COPD, osteoporosis, arthritis) in the ALSWH with moderate to good agreements between women's self-reported diagnosis and hospital records or registry data (Parkinson *et al*., 2013; Peeters *et al*., 2013; Lazarevic *et al*., 2015). We defined the incidence of multimorbidity as the survey at which any two or more new conditions were reported.

Menopausal status and ANM

Menopause status was determined based on the responses to survey questions about hysterectomy, oophorectomy, hormone use and menstrual pattern between (including pre-menopausal, peri-menopausal or postmenopausal) S1 (1996) and S6 (2010) and categorized into surgical menopause (hysterectomy, oophorectomy or both), natural menopause or hormone use (Mishra and Dobson, 2012).

ANM was confirmed by at least 12 months of cessation of menses where this was not the result of an intervention (e.g. surgical menopause). If ANM was reported at multiple surveys, data reported at the last available survey was used. The timing of ANM was categorized as ≤40 (premature menopause), 41–45 (early menopause), 46–49, 50–51, 52–53 and ≥54 years (Mishra *et al*., 2017).

Confounders

We chose confounders based on the scientific literature, including reproductive variables (e.g. parity), socioeconomic status (e.g. education, country of birth) and health behaviour factors (e.g. body mass index, physical activity and smoking). These variables were associated with the development of chronic conditions and multimorbidity (van Dijk *et al*., 2015; Xu *et al*., 2017; Matulonga-Diakiese *et al*., 2018; Xu *et al*., 2019) and were related to timing of menopause (Mishra *et al*., 2017). From the reported menopausal hormone therapy (MHT) status at each survey between S1 and S6, we derived 'ever use of MHT' (yes or no). Number of children (parity) was obtained at S1 (categorized as no children, 1 and ≥2). Education was obtained at S1 (classified into university/higher degree, trade/apprenticeship/diploma, high school certificate or no qualifications). BMI was calculated as weight in kilograms divided by height in metres squared and was estimated at each survey and categorized (underweight [<18.5 kg/m^2], normal weight [18.5–24.9 kg/m^2], overweight [25–29.9 kg/m^2] or obese [≥30 kg/m^2]) (World Health Organization, 2000). Physical activity was asked at each survey and was categorized into sedentary (0–39 metabolic equivalent [MET] min/week), low (40–599 MET min/week), moderate (600–1199 MET min/week) or high (≥1200 MET min/week) (Brown *et al*., 2004). Smoking status was asked at each survey and was categorized into never smoked, ex-smoker or current smoker.

Statistical analysis

Baseline characteristics were described according to (i) the incidence of multimorbidity during the follow-up (2010–2016) and (ii) categories of ANM. Differences between groups were compared using *t*-tests, analysis of variance or chi-square tests.

We assessed the associations between ANM and the development of multimorbidity and individual conditions in a series of models. Firstly, we estimated the associations of ANM with the baseline prevalence and follow-up incidence of multimorbidity in postmenopausal women in both crude and fully adjusted models, respectively. Logistic regression models were used to estimate the prevalence of multimorbidity at S6 (baseline, 2010) in relation to the ANM. Repeated measures logistic regression by generalized estimating equation (GEE) models were used to estimate the incidence of multimorbidity between S7 and S8 (follow-up, 2010–2016) in relation to the ANM. In the fully adjusted models, time-varying covariates (BMI, physical activity and smoking) were included from the previous survey. We also tested whether there is a nonlinear association between ANM and prevalence and incidence of multimorbidity by adding a quadratic term of continuous ANM to the models. Secondly, the same set of models from the first step was performed to estimate the associations of ANM with the prevalence and incidence of individual conditions (Supplementary Table SI). As a small number of cases occurred for some conditions, only crude models were performed. ANM of 50–51 was the reference group for all analyses.

Sensitivity analyses

We performed two sets of additional analyses to check the robustness of our findings. We re-ran all models in the main analyses by including (i) women who have never used MHT and (ii) women who were condition free at baseline (S6, 2010).

SAS (version 9.4, SAS Institute Inc.) was used for all analyses. All statistical tests were two-sided, and $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics of participants according to ANM and the development of multimorbidity

Among 5107 women included for the analyses of the associations between ANM and the development of multimorbidity at baseline (S6, 2010), 119 (2.3%) women reported experiencing premature menopause (Table I). Women who experienced premature menopause were more likely to have more chronic conditions, to previously used MHT, to be nulliparous, to be less educated, to be obese, to have low levels of physical activity and to be smokers.

Over 6 years of follow-up, 2814 (55.1%) women developed multimorbidity (Table II). Women who developed multimorbidity were more likely to have previous use of MHT, to be less educated, to be obese, to have low levels of physical activity and to be smokers.

ANM and the development of multimorbidity and individual chronic conditions

Premature menopause was associated with increased odds of multimorbidity for both baseline prevalence (S6, 2010) and follow-up incidence (S7–8, 2010–2016) (Table III). The ORs for the association between premature menopause and prevalence of multimorbidity were 3.57 (95% CI 1.39 to 9.19) and 1.98 (95% CI 1.31 to 2.98)

Table 1 Baseline characteristics of participants (%) according to age at natural menopause ($n = 5107$), Australian Longitudinal Study on Women's Health (ALSWH) 2010.

Characteristic	Age at natural menopause						P[a]
	≤40 ($n = 119$)	41–45 ($n = 456$)	46–49 ($n = 740$)	50–51 ($n = 1207$)	52–53 ($n = 1009$)	≥54 ($n = 1576$)	
Age, years[b]	61.5 (1.4)	61.6 (1.4)	61.6 (1.4)	61.4 (1.4)	61.6 (1.4)	61.6 (1.5)	0.0787
Age at natural menopause, years[b]	38.2 (2.4)	43.9 (1.3)	47.8 (1.0)	50.3 (0.4)	52.4 (0.5)	55.7 (1.6)	<0.0001
Number of chronic conditions	2.6 (1.9)	2.1 (1.7)	2.1 (1.6)	2.0 (1.6)	1.8 (1.5)	2.0 (1.6)	<0.0001
Ever MHT users[c]	42.0	36.6	32.0	27.3	26.3	28.0	<0.0001
Parity distribution							0.0045
No child	11.5	9.8	11.3	8.5	7.6	7.9	
One child	15	7.2	10.5	8.0	7.4	8.0	
≥2 children	73.5	82.9	78.3	83.5	85.1	84.1	
Education							0.0072
University/higher degree	8.6	13.7	17.0	16.3	19.1	19.9	
Trade/apprenticeship/diploma	18.8	22.3	19.8	21.9	23.2	21.2	
High school certificate	18	15.5	18.2	16.7	16.8	17.7	
No qualifications	54.7	48.6	45	45.1	41	41.2	
Country of birth							0.6681
Australia	79.1	75.6	76.7	76.5	77.1	78.7	
Outside Australia	20.9	24.4	23.3	23.5	23	21.3	
BMI categories							0.0018
Underweight (<18.5 kg/m^2)	2.6	1.4	2.2	1.9	0.9	0.8	
Normal weight (18.5–24.9 kg/m^2)	26.3	43.2	39.4	38.3	40.1	36.1	
Overweight (25–29.9 kg/m^2)	36.0	33.0	33.3	34.7	35.1	34.1	
Obese (≥30 kg/m^2)	35.1	22.5	25	25.2	23.9	29.0	
Physical activity							0.0096
High (≥1200 MET min/week)	37.8	35.6	33.8	38.6	36.6	36.9	
Moderate (600–1199 MET min/week)	12.6	19.7	20.4	22.0	23.7	23.5	
Low (40–599 MET min/week)	25.2	28.4	29.9	26.3	27.7	26.5	
Nil/sedentary (0–39 MET min/week)	24.3	16.4	15.9	13.1	12.1	13.0	
Smoking status							<0.0001
Never	50.9	55.0	57.5	61.6	62.9	64.9	
Ex-smoker	33.9	31.1	30.8	31.0	29.8	28.6	
Current	15.3	13.8	11.7	7.4	7.3	6.5	

[a]Analysis of variance was used for continuous variable; chi-squared analyses were used for categorical variables.
[b]Data are presented as mean (standard deviation).
[c]Of until S6 (2010).
MHT, menopausal hormone therapy; BMI, body mass index; MET, metabolic equivalent of task.

in the crude and fully adjusted models, compared with those who experienced natural menopause at age 50–51 years. The ORs for the association between premature menopause and incidence of multimorbidity were 3.15 (95% CI 1.82 to 5.45) and 3.03 (95% CI 1.62 to 5.64) in the crude and fully adjusted models, compared with those who experienced natural menopause at age 50–51 years. There was evidence of non-linear relationships between ANM and prevalence and incidence of multimorbidity ($P_{quadratic}$: 0.0127 and 0.0360).

Similar results were observed for individual conditions. For example, women with premature menopause had the highest prevalence and incidence of most of the 11 conditions except for the incidence of stroke (Supplementary Table SI). The sensitivity analyses also showed the similar results (Supplementary Tables SII and SIII).

Discussion

Principal findings

Based on data from this national prospective cohort of mid-aged to early elder women, we found that more than half of women experienced multimorbidity in their postmenopausal life. Women with premature menopause had almost three times higher odds of devel-

Table II Baseline characteristics of participants (%) according to the number of chronic conditions developed during 6 years of follow-up ($n = 5107$), Australian Longitudinal Study on Women's Health (ALSWH) 2010.

Characteristic	No. of chronic conditions		P[a]
	0 or 1 ($n = 2293$)	≥2 ($n = 2814$)	
Age, years[b]	61.5 (1.4)	61.6 (1.5)	0.0011
Age at natural menopause, years[b]	51.4 (4.0)	51.0 (4.5)	0.0005
Ever MHT users[c]	23.1	34.2	<0.0001
Parity distribution			0.4234
No child	8.2	9.1	
One child	8.1	8.5	
≥2 children	83.7	82.3	
Education			0.0005
University/higher degree	19.1	16.4	
Trade/apprenticeship/diploma	21.3	21.8	
High school certificate	18.7	15.9	
No qualifications	40.9	45.8	
Country of birth			0.5451
Australia	76.9	77.6	
Outside Australia	23.1	22.4	
BMI categories			<0.0001
Underweight (<18.5 kg/m^2)	1.6	1.2	
Normal weight (18.5–24.9 kg/m^2)	46.1	31.9	
Overweight (25–29.9 kg/m^2)	34.6	34.0	
Obese (≥30 kg/m^2)	17.7	32.9	
Physical activity			<.0001
High (≥1200 MET min/week)	41.6	32.7	
Moderate (600–1199 MET min/week)	22.1	22.3	
Low (40–599 MET min/week)	25.5	28.8	
Nil/sedentary (0–39 MET min/week)	10.9	16.2	
Smoking status			<0.0001
Never	65.7	58.0	
Ex-smoker	27.1	32.5	
Current	7.2	9.5	

[a]Independent-samples *t*-test was used for continuous variable (age); chi-squared analyses were used for categorical variables.
[b]Data are presented as mean (standard deviation).
[c]Of until S6 (2010).
MHT, menopausal hormone therapy; BMI, body mass index; MET, metabolic equivalent of task.

oping multimorbidity in their 60s, adjusted for number of chronic conditions at baseline and related risk factors. Additionally, women with premature menopause also experienced a higher incidence of most of the 11 individual conditions.

Strengths and limitations

The strengths of our study included the large sample size, long follow-up and nationally representative study population, which improves the generalizability of our findings to other middle-aged women. In addition, the extensive survey data collected from the women has also allowed adjustment for a wide range of cofounders, including known risk factors for menopause and chronic conditions.

However, our results should be considered in the context of some limitations. First, menopausal transition and disease diagnosis relied on self-reported information. Previous studies have demonstrated the validity of most of the chronic conditions (Brown *et al*., 2004; Okura *et al*., 2004; Burton *et al*., 2010; Hansen *et al*., 2014). For example, self-reported diabetes, heart disease and stroke were validated with hospital data in women who were hospitalized in New South Wales, Australia (Navin Cristina *et al*., 2015). The prevalence and bias adjusted kappa for the three conditions were 0.93, 0.91 and 0.98 respectively. The information on cancer has been validated against Cancer Registry data with 89% sensitivity and 97% specificity (Stavrou *et al*., 2011). Second, the results depend, to some extent, on the conditions included in the study. A number of less common conditions, such as chronic

Table III Associations (odds ratios [OR] and 95% CI) of age at natural menopause with the prevalence (baseline, 2010) and incidence (follow-up, 2010–2016) of multimorbidity in postmenopausal women ($n = 5107$), Australian Longitudinal Study on Women's Health (ALSWH).

	Age at natural menopause						
	≤40 ($n = 119$)	41–45 ($n = 456$)	46–49 ($n = 740$)	50–51 ($n = 1207$)	52–53 ($n = 1009$)	≥54 ($n = 1576$)	$P_{quadratic}$[a]
Baseline (2010)							
No. and % of cases	84 (70.6)	266 (58.3)	427 (57.7)	662 (54.9)	526 (52.1)	849 (53.9)	
Crude model[b]	3.57 (1.39, 9.19)	1.77 (0.85, 3.71)	0.80 (0.36, 1.79)	Ref	0.72 (0.34, 1.53)	0.84 (0.44, 1.59)	0.0127
Fully adjusted model[c]	1.98 (1.31, 2.98)	1.15 (0.92, 1.42)	1.11 (0.92, 1.34)	Ref	0.89 (0.75, 1.05)	0.95 (0.82, 1.11)	
Follow-up (2010–2016)							
No. and % of cases	53 (44.5)	187 (41.0)	323 (43.6)	487 (40.4)	392 (38.9)	631 (40.0)	
Crude model[d]	3.15 (1.82, 5.45)	1.02 (0.66, 1.59)	1.51 (1.07, 2.11)	Ref	1.13 (0.81, 1.57)	1.15 (0.86, 1.55)	0.0360
Fully adjusted model[e]	3.03 (1.62, 5.64)	0.96 (0.58, 1.58)	1.35 (0.93, 1.98)	Ref	1.20 (0.84, 1.73)	1.23 (0.89, 1.71)	

[a] $P_{quadratic}$: a quadratic term of the age at natural menopause (continuously) was added in the age-period adjusted model to test whether a nonlinear association was present.
[b] Adjusted for age at S6 (2010).
[c] Adjusted for age at S6 (2010), parity, ever menopausal hormone (MHT) users, education, country of birth, body mass index, physical activity and smoking status.
[d] Adjusted for age at S6 (2010), survey years (S7–8) and number of chronic conditions at S6 (2010).
[e] Adjusted for age at S6 (2010), survey years (S7–8) and number of chronic conditions at S6 (2010), parity, ever MHT users, education, country of birth, body mass index, physical activity and smoking status.

kidney disease and dementia, were not included. Additionally, since the study is limited to Australian women, these findings should be replicated in other populations.

Interpretation

Possible mechanisms for the findings

There are several plausible explanations for the associations between premature menopause and the development of multimorbidity. Firstly, our study suggested that women who experienced natural premature menopause and women who developed multimorbidity shared most of the reproductive, socioeconomic and health behavioural risk factors. These risk factors and others (e.g. genetic and environmental factors) may drive the earlier onset of both menopausal transition and chronic conditions (Levine *et al*., 2016; Mishra *et al*., 2017; Rocca *et al*., 2018). Secondly, some chronic conditions (e.g. depression) or pre-conditions (e.g. insulin resistance, high level of cholesterol) in premenopausal women were positively associated the onset of menopause, further leading to the onset of other related chronic conditions (Kok *et al*., 2006; Li *et al*., 2016; Muka *et al*., 2017). Thirdly, the genetic predisposition to earlier ANM itself may play an important role; for example, a recent study suggested that genetic variants associated with earlier ANM are associated with increased cardiovascular risk (Sarnowski *et al*., 2018). Finally, premature estrogen loss itself, either naturally occurring or induced by surgery, causes an alteration of several fundamental ageing processes at the cellular, organ and system level, finally leading to the onset of chronic conditions and multimorbidity (Levine *et al*., 2016; Rocca *et al*., 2018).

Comparison with other studies

To the best of our knowledge, this is the first population-based prospective cohort study to examine the association between ANM and the development of multimorbidity. The observed increased odds of individual chronic conditions among women in the premature or early menopause in the present study are in line with what has been reported in previous studies. These conditions include diabetes, cardiovascular disease, chronic lung disease, depression, anxiety, arthritis, osteoporosis and breast cancer (Faubion *et al*., 2015; Muka *et al*., 2016; Muka *et al*., 2017; Campbell *et al*., 2018; Pandeya *et al*., 2018; Xu *et al*., 2018). However, because of the small number of the individual chronic condition events, some of the findings did not reach statistical significance. Further large cohort studies or pooled cohort studies are needed to validate these findings (Mishra *et al*., 2013).

Implications of findings

Related to menopausal transition, many chronic conditions occur or develop in mid-aged and elderly women—usually around the age of 60 (Lobo *et al*., 2014; van Dijk *et al*., 2015). Recent data showed that multimorbidity might be a marker of acceleration of the ageing process and related to pathways linked to longevity (Fabbri *et al*., 2015; Fabbri *et al*., 2016; Rocca *et al*., 2018). Although not surprisingly, premature menopause was associated with increased risk of both individual conditions and multimorbidity, our findings add value by emphasizing that multimorbidity should be considered as a clinical and public health priority for chronic condition control and prevention in women's health. This finding supports previous recommendations that a common solution and comprehensive strategy for prevention and management of these chronic conditions and multimorbidity is needed (Lobo *et al*., 2014; Jaspers *et al*., 2015; van Dijk *et al*., 2015). Particularly, the first 10 years after menopause (e.g. before the age of 60 years) is recommended as an important window for intervention (Lobo *et al*., 2014). However, out study suggested that women with premature menopause experienced increased odds of developing multimorbidity in their 60s. Hence, this life stage is also critical for women with premature menopause. Further studies to

confirm which conditions emerge earlier and to elucidate what kind of solutions could potentially prevent the onset of other chronic conditions around menopausal transition or during postmenopausal life are warranted.

The common solutions and the comprehensive strategy for prevention and management of these chronic conditions and multimorbidity includes nutritional and lifestyle change (diet, exercise), controlling of body weight, mentally stimulating activity and regular screening for cancer and other reproductive conditions (Lobo *et al*., 2014; van Dijk *et al*., 2015; Xu *et al*., 2019). The well-identified risk factors from our study for early onset of natural menopause could also identify high-risk postmenopausal women who may benefit from reproductive health-related screening and risk factors assessment at an earlier age. Recent studies also suggested that Mendelian randomization (MR) presents an opportunity to explore causal relationships between these risk factors (including reproductive factors) and chronic diseases, particularly in women as they are disproportionately affected by common diseases (Censin *et al*., 2019). However, MR studies have mostly focused on a single condition rather than multimorbidity (Neumeyer *et al*., 2018; Sarnowski *et al*., 2018; van der Plaat *et al*., 2019). For example, one study found that a one-unit decrease in genetically predicted ANM increases the hazard of coronary heart disease death by 12% and of the composite endpoint by 10% in women (Sarnowski *et al*., 2018); the other study suggested that age at menopause was not associated with colorectal cancer (Neumeyer *et al*., 2018). More MR analyses are needed to explore the causal associations between menopause and other chronic conditions and multimorbidity as more genetic data is now available (Censin *et al*., 2019).

Conclusions

Our findings indicate multimorbidity is common in mid-aged and early elderly women. Premature menopause is associated with increased odds of developing multimorbidity, adjusted for previous chronic conditions and for several possible confounders. Additionally, premature menopause is also associated with the higher incidence of individual chronic conditions. Our findings could inform health professionals to consider comprehensive screening and assessment of risk factors for increased risk of multimorbidity when treating women who experienced natural premature menopause. Our findings also highlighted that multimorbidity should be considered as a clinical and public health priority for chronic conditions control and prevention in women's health. Further studies on the mechanisms for these associations between age at menopause and the development of multimorbidity are needed.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

The research on which this paper is based was conducted as part of the ALSWH, managed by the Universities of Queensland and Newcastle. We are grateful to the Australian Government Department of Health for funding and to the women who provided the survey data.

Authors' roles

X.X., M.J. and G.D.M. contributed to the design of the study. X.X. conducted the data analysis. X.X. and G.D.M. performed the interpretation of the data. X.X. drafted the manuscript. X.X., M.J. and G.D.M. revised the article and approved the final version to be published.

Funding

The ALSWH was supported by the Australian Government Department of Health. X.X. is funded by an International Postgraduate Research Scholarship from the Australian government and a UQ Centennial Scholarship from The University of Queensland. G.D.M. is supported by the National Health and Medical Research Council Principal Research Fellowship (APP1121844).

Conflict of interest

None.

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