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Is premature ovarian insufficiency associated with mortality? A three-decade follow-up cohort

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ABSTRACT

Objective: To evaluate the association between premature ovarian insufficiency (POI) and mortality.
Materials and methods: This was a secondary analysis of a long-term cohort of Chilean women who received preventive health care between 1990 and 1993. The exposure variable was POI and the outcome was death, and follow-up time was 30 years. Patient data were extracted from medical records. Data related to deaths were obtained from the records of the official government registry as of January 2021. Cox regression proportional hazard models were used to estimate crude and adjusted hazard ratios (HR) and 95 % confidence intervals (CI).
Results: Data for a total of 1119 women were included in the analysis. Median age was 47 years (interquartile range: 44–52). The baseline prevalence of POI was 6.7 %. At the end of the follow-up, 34.7 % of women with POI had died, compared with 19.3 % of women without the condition ($p < 0.001$). A larger proportion of women with POI died from cardiovascular disease (12.0 % vs. 5.1 %; OR: 2.55, 95 % CI: 1.21–5.39) whereas there was no significant difference in cancer mortality (6.7 % vs. 7.7 %; OR: 0.86, 95 % CI: 0.34–2.19). In the adjusted Cox model, POI was among the main factors associated with mortality (hazard ratio [HR] 1.60, 95 % CI: 1.03–2.47), after diabetes (HR 2.51, 95 % CI: 1.40–4.51) and arterial hypertension (HR 1.75, 95 % CI: 1.29–2.37).
Conclusion: Although POI affects a small group of women, its association with mortality seems to be relevant; hence it is necessary to implement measures that reduce this risk.

1. Introduction

There has been a significant increase in the life expectancy worldwide in the past century. In 1900, global average lifespan was just 31 years, and below 50 years in even the richest countries [1]. Due to the fact that in most countries life expectancy has exceeded 50 years (age when ovaries cease hormone production) women will live a significant period of their lives deprived of ovarian steroids [2].

Estrogen receptors (ERs) are located not only in the female reproductive tract and breast, but also in the brain, bone, liver, colon, skin, and salivary gland [3]. Estrogen deficiency caused by the menopause will mainly impact the central nervous system producing a series of symptoms that deteriorate female quality of life; but, in addition, directly or indirectly it is associated with chronic conditions such as obesity, the metabolic syndrome, diabetes, cardiovascular disease, osteoporosis, osteoarthritis, cognitive decline, dementia, depression, and cancer [4,5].

Multimorbidity is a health condition defined by the co-existence of at least two chronic diseases in the same individual, affecting their quality of life and increasing mortality [6]. Women with premature ovarian insufficiency [POI] experience a higher prevalence of several chronic conditions. Compared to women who have experienced menopause at age 50–51, those with POI have twice the odds of experiencing multimorbidity by age 60 [7,8].

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A meta-analysis of seven cohorts, showed that women with POI had a higher risk ratio [RR] of death from all causes (RR 1.39; 95 % CI: 1.10–1.77); however, none of the meta-analyzed studies exceeded 20 years of follow-up. A systematic review that identified 32 studies that included 310,329 women showed that those who experienced menopause younger than 45 years had a higher risk for all-cause mortality compared to women presenting menopause at 45 or older (RR 1.12 95 % CI, 1.03–1.21) [9,10].

The aim of the present study was to evaluate the association between POI and mortality, which will allow us to compare our results with those of previous publications and check if the risk of death associated with early menopause differs with a longer follow-up than that of studies previously reported [9,10]. Our study will provide data that allow us to evaluate the need to implement measures that reduce the possible risk of mortality in women with early menopause.

2. Methods

2.1. Study design and population

This is a secondary analysis of a prospective cohort study conducted at the Southern Metropolitan Health Service of the Barros Luco Hospital, Santiago de Chile, Chile. This study recruited women who attended preventive medicine controls between October 1990 and March 1993. During this period, a total of 1204 women aged 40 to 59 were invited to participate, of whom 1159 (95.1 %) agreed [11]. The following information was collected at baseline: demographics (RUT, unique number that identifies people in Chile, date of birth, date of evaluation, occupation, years of education); clinical (diabetes, hypertension); anthropometrics (height, weight); systolic/diastolic blood pressure; menopausal status; laboratory findings (fasting blood lipids and glucose levels); the use of medication for dyslipidemias (yes/no); total physical activity (minutes per week) and, total smoked cigarettes per week.

2.2. Laboratory assays

Total cholesterol and triglyceride levels were measured using enzymatic colorimetric methods (Sigma Chemical Co, St. Louis, Missouri, USA). Intra and inter-assay coefficients variations for total cholesterol, high density lipoprotein cholesterol (HDL—C) and triglycerides were 1.6 % and 3.9 %; 3.9 % and 4.2 %; and 4.6 % and 3.9 %, respectively. Low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula. Glucose was measured with colorimetric methods (Hexokinase, Sigma Chemical Co, St. Louis, Missouri, USA) with intra- and inter-assay coefficient variations of 0.7 % and 1.2 %, respectively.

2.3. Exposure variables

For the analysis we included the following baseline exposure variables: obesity (body mass index [BMI], $\geq$ 0 kg/m^2); postmenopausal status ($\geq$ 12 months of amenorrhea); sedentary lifestyle ($\leq$ 150 min of physical activity per week); unskilled jobs (without university or technical education); type 2 diabetes mellitus (fasting blood glucose $\geq$126 mg/dL on two measurements or $\geq$200 mg/dL at 2 h after an overload of 75 g of glucose and/or the use of hypoglycemic drugs with the previous diagnosis of type 2 diabetes mellitus); and hypertension (systolic/diastolic blood pressure $\geq$140/90 mmHg and/or the use of antihypertensive drugs). Lipid abnormalities included: (i) hypertriglyceridemia (fasting serum triglyceride level $\geq$150 mg/dL), (ii) reduced HDL-C ($\leq$ 50 mg/dL), (iii) high LDL-C ($\geq$ 130 mg/dL) and (iv) high total cholesterol ($\geq$ 200 mg/dL or 6.2 mmol/L), as defined by NCEP ATP III [12]. POI was defined as amenorrhea of more than a year in women <40 years of age [13].

2.4. Outcome

On December 2020, using the national identification number (RUT from Spanish acronym), we consulted the vital status (alive or dead, and date of death) of each woman using the Official Government records [14]. Survival time for each woman time was calculated by means of this information. In Chile, an official death certificate is required to bury a dead person. This document is certified by a physician, and it includes the cause of death in 99 % of cases [15].

2.5. Statistical analysis

2.5.1. Exploratory and descriptive analysis

The distribution of numerical and categorical variables was explored using analytical and graphical methods. Numerical variables are presented as medians (interquartile range [IQR]) and ranges (minimum and maximum values); whereas categorical variables as absolute frequencies (n) and percentages (%). We used the reverse Kaplan-Meier method to estimate the median of follow-up time [16].

2.5.2. Association between POI and covariates

The associations between POI and relevant demographics, clinical, anthropometric, laboratory and life style/habits variables were appropriately tested using the Mann-Whitney U test, chi-square test of independence or the Fisher's exact test.

2.5.3. Association between POI and mortality

Bivariate analysis compared survival curves estimated through the Kaplan-Meier product-limit method [17]. Crude hazard rate ratios [HR] were estimated through simple Cox proportional hazard model regressions. Also, we performed multiple Cox proportional hazard regression analyses to estimate adjusted HR for all-cause mortality. We selected certain baseline variables for the adjustment based on their theoretical role as potential confounders of the association of interest. To avoid drawbacks of categorization [18,19], we directly modelled age, LDL-C, HDL—C, triglycerides levels and number of cigarettes per week as numerical variables. Also, we reported adjusted survival curves for the overall survival of women with POI versus women without POI. We obtained adjusted survival curves fixing categorical variables at 0 (reference value) and numerical values in their average values. We reported the p-values of the likelihood-ratio test and 95 % confidence interval (95 % CI).

2.5.4. Model assumptions

We evaluated linearity using two complementary approaches: multivariate fractional polynomial modelling (MFPM) [20,21] and visual inspection of smoothed martingale residual plots. We set the MFPM algorithm to search non-linear transformations from numerical variables until four degrees of freedom using a closed test procedure with a significance level of 5 %. Proportional hazard assumption was assessed through plotting and the inspection of Schoenfeld residuals versus time, and also by means of the Grambsch and Therneau's non-proportionality test [22]. Outliers were assessed using deviance residuals against time. Diagnostic of influential points was done through DFBETAS versus time plots. Finally, we used Cox-Snell residual plots to assess goodness of fitness of the final model. All statistical analyses were conducted using R version 4.1.0 (R Core Team 2021, Vienna, Austria) and Stata/SE 17.0 for Windows 10 Pro x86–64 bits (StataCorp, College Station, Texas, USA). For all calculations a p value of <0.05 was considered as statistically significant.

2.6. Ethical considerations

The ethical committee of the Southern Metropolitan Health Service (Santiago de Chile, Chile) approved the protocol of the original cohort. The study was carried in accordance to the Declaration of Helsinki. All

women provided signed consent to participate after being informed of the study and its aims.

3. Results

3.1. Characteristics of the study population

In total, 1159 women were assessed in the baseline of the cohort study and were assessed for eligibility for this secondary analysis. We only included women with a diagnosis of non-surgical menopause (1119/1159, 96.5 %). As calculated by the reverse Kaplan-Meier method, median (IQR) follow-up time for all participants was 29.2 years (28.6–29.7).

Table 1 summarizes the characteristics of women included in this analysis (all and according to the presence of POI). Median age was 47 years (IQR: 44–52; range 39–71). Prevalence of POI at baseline was 6.7 % (75/1119, 95 % CI 5.3–8.3). For the entire cohort selected for this analysis, overall survival at 10 years was 97.4 % (95 % CI 96.3–98.2), and the 30 year overall survival was 78.5 % (95 % CI 75.7–81.0).

3.2. Association between POI and covariates

At baseline, women with POI were significantly older (50 vs. 47 years, $p < 0.001$), and less educated (78.7 % vs 64.1 %, $p = 0.010$). On the other hand, women without POI reported a higher rate of contraceptive use than women with POI (55.5 % vs. 30.7 %, $p < 0.001$), sedentary lifestyle (93.4 % vs. 86.7 %, $p = 0.028$) and lower median triglycerides levels (115 vs. 135 mg/dL, $p = 0.030$) than POI women (Table 1).

3.3. Association between POI and mortality

It was possible to verify vital status of all women included for analysis by December 31st 2021. At the end of the follow-up, 20.3 % of the women (227/1119) had died. More women POI died as compared to non-POI ones (34.7 % [26/75] vs. 19.3 % [201/1044], $p < 0.001$) (Table 1). One hundred and fifty-two women (67.0 %) had died of cancer or cardiovascular disease. Women with POI died more from cardiovascular diseases than non-POI women (12.0 % vs. 5.1 %; OR: 2.55, CI 95 %: 1.21–5.39); in contrast there was no significant difference in cancer mortality (6.7 % vs 7.7 %, respectively; OR: 0.86, 95 % CI: 0.34–2.19).

Crude and adjusted overall survival curves were statistically different for women with POI as compared to those without POI (Fig. 1A and Fig. 1B). Crude and adjusted hazard ratios (cHR and aHR) for death was 1.97, 95 % CI: 1.30–3.0 and, 1.60, 95 % CI: 1.03–2.47, respectively. The complete-case analysis excluded four women (0.4 %) due to missing HDL-C or LDL-C levels for the multivariate analysis.

Only 45 women of the total cohort used MHT (4.0 %). Of the 75 women with POI, there were 6 MHT users of whom 2 died during follow-up (33 %). Among the 69 non MHT users there were 24 deaths (34.8 %). In Table 2, crude and adjusted regressions show that women with POI had a higher all-mortality risk than women without POI. Specifically, hazard rates for death were 97 % higher in the POI group than in the group without POI (cHR = 2.02, 95 % CI: 1.34–3.04, $p = 0.002$). The magnitude of this association was slightly reduced after adjusting for potential confounders (aHR = 1.60, 95 % CI: 1.03–2.47, $p = 0.036$).

Table 1
Baseline characteristics of women selected for the analysis.

Parameters	Overall, $n = 1119$	Premature ovarian insufficiency		p value*
		No, $n = 1044$	Yes, $n = 75$	
Age at enrollment				
Median (IQR)	47.0 [8.0]	47.0 [8.0]	50.0 [9.5]	<0.001
Range	39.0–71.0	39.0–71.0	41.0–61.0	
Older age at enrollment				
<48 years	570 (50.9)	545 (52.2)	25 (33.3)	0.002
≥48 years	549 (49.1)	499 (47.8)	50 (66.7)	
Lower educational level	728 (65.1)	669 (64.1)	59 (78.7)	0.010
Has a partner	744 (66.5)	705 (67.5)	39 (52.0)	0.006
Body mass index (kg/m^2)				
Median	25.3 [5.3]	25.3 [5.3]	25.5 [5.0]	0.4
Range	16.8–45.7	16.8–45.7	20.3–38.9	
Total smoked cigarettes per week				
Median	0.0 [21.0]	0.0 [21.0]	0.0 [37.5]	0.3
Range	0.0–420.0	0.0–290.0	0.0–420.0	
Obesity (BMI > 30 kg/m^2)	169 (15.1)	155 (14.8)	14 (18.7)	0.4
Sedentary lifestyle	1040 (92.9)	975 (93.4)	65 (86.7)	0.028
Type-2 diabetes mellitus	29 (2.6)	25 (2.4 %)	4 (5.3)	0.12
High blood pressure	193 (17.2)	181 (17.3)	12 (16.0)	0.8
Hormonal contraceptive use	602 (53.8)	579 (55.5)	23 (30.7)	<0.001
Number of pregnancies				
Median	3.0 [3.0]	3.0 [3.0]	3.0 [4.0]	>0.90
Range	0.0–20.0	0.0–20.0	0.0–14.0	
Number of abortions				
Median	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	1.0 [0.0, 1.0]	0.062
Range	0.0–12.0	0.0–10.0	0.0–12.0	
Triglycerides (mg/dL)				
Median	115.0 [86.0, 157.5]	115.0 [86.0, 157.0]	135.0 [92.5, 185.5]	0.030
Range	36.0–984.0	36.0–984.0	56.0–388.0	
High triglyceride level	325 (29.0)	295 (28.3)	30 (40.0)	0.030
LDL-C (mg/dL)				
Median	138.2 [43.0]	138.0 [53.8]	143.6 [44.2]	>0.9
Range	28.6–349.6	28.6–349.6	55.2–289.2	
Missing data	4	2	2	
High LDL-C	986 (88.1)	919 (88.0)	67 (89.3)	0.7
HDL-C (mg/dL)				
Median	51.0 [17.0]	51.0 [17.0]	49.0 [21.0]	0.8
Range	23.0–99.0	23.0–98.0	30.0–99.0	
Missing data	4	2	2	
Low HDL-C level	515 (46.0)	478 (45.8)	37 (49.3)	0.6
Death	227 (20.3)	201 (19.3)	26 (34.7)	0.001

Data are presented as medians [interquartile range (IQR)], ranges or frequencies n percentages (%); * p values as determined by the Mann-Whitney U test, the Pearson's chi-squared test and/or Fisher's exact test; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL—C, high density lipoprotein cholesterol.

4. Discussion

Our cohort shows, like other similar ones analyzed in a meta-analysis [9], that POI is associated to an increased risk of mortality. However, the present study found a higher risk than that described in the aforementioned study (1.60; 95 % CI 1.03–2.47 vs. 1.39, 95 % CI 1.10–1.77). Despite this difference, it should be noted that results may vary according to the studied population. In the mentioned meta-analysis, subgroup analyses indicated that there was no significant relationship between POI and all-cause mortality among Norwegians, but a significant relationship was found for Japanese and American women. Also, the greater risk observed in our study may be related to the longer follow-up period compared to those previously mentioned. The risk of mortality, as observed in our survival curves (Fig. 1), shows no difference between women with or without POI in the first decade of follow-up, but they diverge at the longer follow-up.

Regarding the causes of death, we observed a higher cardiovascular

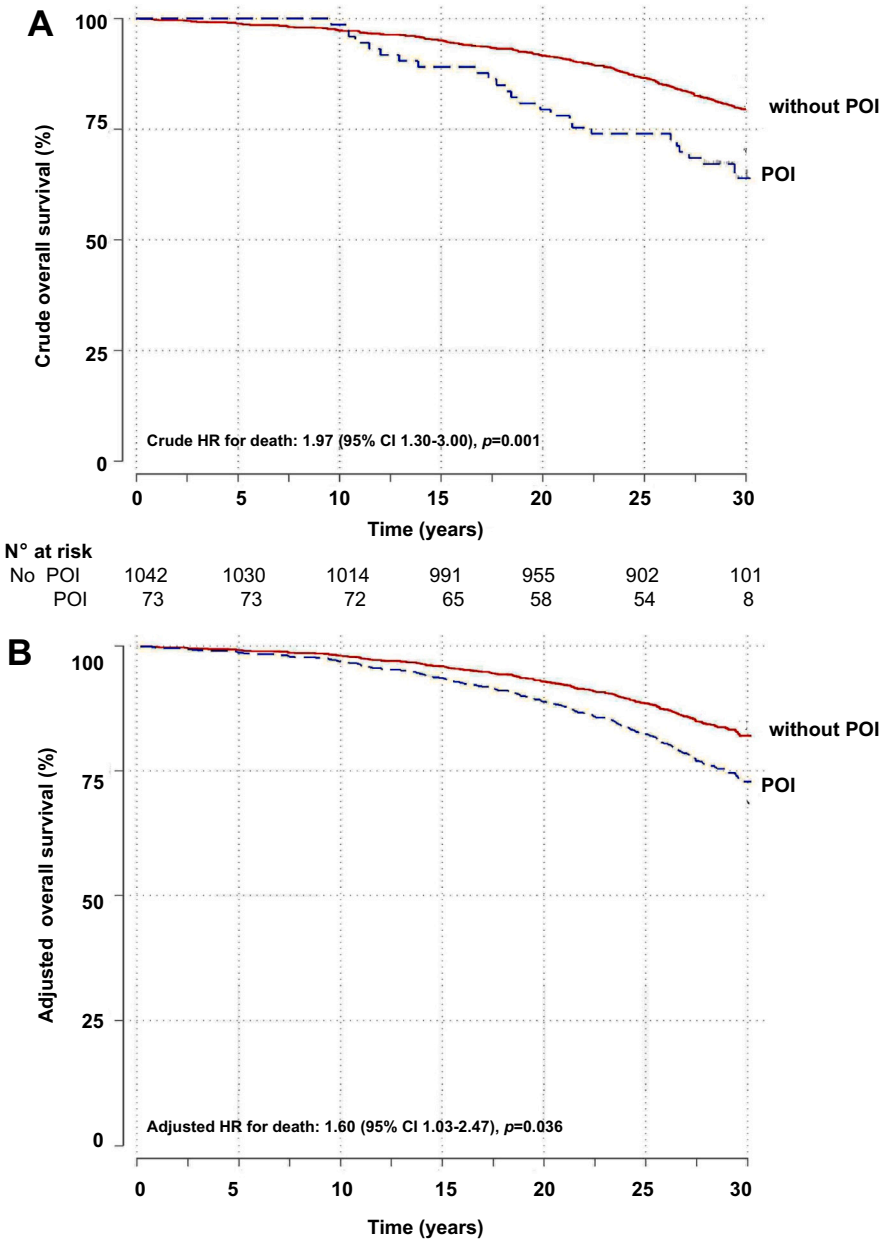

Fig. 1. (A) Crude and (B) adjusted overall survival in women with premature ovarian insufficiency (POI) as compared to those without POI.

mortality in women with POI compared to those without POI. This result is consistent with a systematic review and meta-analysis that noted that POI was related to an increased risk of developing or dying from cardiovascular diseases (HR 1.61, 95 % CI 1.22–2.12) [23]. A recent review regarding cardiovascular risk in women with POI points out to the unfavorable lipid profile, increased abdominal fat, insulin resistance and bleeding disorders that women with POI present as factors associated to a higher cardiovascular risk [24]. Our study shows that lower educational level and elevated triglycerides are more prevalent in women with POI; both characteristics have been reported as cardiovascular risk factors. A meta-analysis of 72 cohorts from Europe, USA, and Asia shows that the risk of cardiovascular death among low and medium versus high education was 1.21 (95 % CI 1.12–1.30) [25]. Regarding triglycerides, a study including 726,030 participants shows that the pooled RRs for cardiovascular disease (CVD) mortality for the lowest (< 90 mg/dL), borderline-high (150–199 mg/dL), and high triglyceride (≥ 200 mg/dL) groups were 0.83 (95 % CI 0.75 to 0.93), 1.15 (95 % CI 1.03 to 1.29), and 1.25 (95 % CI 1.05 to 1.50), respectively [26].

Although we do not have randomized, double-blind, controlled studies evaluating a positive effect of menopausal hormone therapy on mortality risk in women with POI, a study based on the analysis of 386 women with POI, using the Framingham 30-year risk of CVD, estimated that prolonged estrogenic deprivation is associated with an increase of CVD (0.18–0.20 % per year), whereas prolonged estrogen exposure is associated with a reduced risk (0.15–0.16 % per year) [27]. The authors concluded that these results support the policy of early and continued use of estrogen replacement therapy in women with POI. Notably, in the 2018 guidelines of the American College of Cardiology/American Heart Association POI is considered a risk factor for CVD, that requires statin therapy in adults aged 40–75 years who do not have diabetes and have a calculated 10-year cardiovascular risk of 7.5–19.9 % [28]. Therefore, it is essential that women with POI receive hormonal treatment to help prevent the development of CVD, and that this treatment should continue at least until the normal age of menopause onset [24].

In our study we did not find an increase in cancer mortality among POI women. Although some studies show that early menopause

Table 2
Factors associated to death.

Parameters	Crude model			Adjusted model		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Premature ovarian insufficiency	2.02	1.34–3.04	0.002	1.60	1.03–2.47	0.045
Age at enrollment	1.10	1.08–1.13	<0.001	1.09	1.06–1.12	<0.001
Lower educational level	1.57	1.17–2.11	0.002	1.37	1.01–1.85	0.039
Has a partner	0.54	0.42–0.71	<0.001	0.69	0.52–0.91	0.009
Smoking (per every 10 cigarettes)	1.04	1.01–1.06	0.011	1.03	1.00–1.05	0.039
Obesity	1.53	1.10–2.11	0.014	1.23	0.88–1.73	0.241
Sedentary lifestyle	1.20	0.70–2.06	0.500	1.16	0.67–2.00	0.588
Type-2 diabetes mellitus	2.84	1.62–4.98	0.002	2.17	1.22–3.86	0.017
High blood pressure	2.17	1.63–2.89	<0.001	1.75	1.29–2.37	<0.001
Hormonal contraceptive use	0.87	0.67–1.13	0.285	1.21	0.91–1.60	0.181
Triglycerides (per every 100 mg/dL)	1.15	0.99–1.33	0.099	1.02	0.83–1.26	0.820
LDL-C (per every 100 mg/dL)	1.08	0.79–1.49	0.629	0.84	0.61–1.15	0.265
HDL-C (per every 10 mg/dL)	1.02	0.92–1.13	0.695	0.98	0.88–1.09	0.720

HR, hazard ratio; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterols.

increases the risk of mortality related to digestive tract cancer, others point to a lower risk of mortality related to breast, uterine and ovarian cancer [29–31]. Therefore, the effect over the risk cancer related mortality would be neutral in women with POI. In this same sense, the meta-analysis of Tao et al. [9] point out that in 4 studies there is a RR for cancer of 1.31 (95 % CI 0.78–2.18).

Our Cox model shows that POI is an important risk factor for mortality, third in position before diabetes mellitus and high blood pressure. Both diseases have important preventive programs practically worldwide, but no similar interest is observed for early menopause. Moreover, many women with POI are not on menopausal hormone therapy. In this sense, one study shows that 32 % of women never took hormone therapy, 19 % started it years after POI diagnosis, and 4 % stopped it prior to 45 years of age [32]. As a result, these women will have a higher risk of morbidity and mortality. There is an urgent need to insist on the education of healthcare providers and the general population in order to minimize the risks related to POI.

Regarding the limitations of our study, one can mention its observational nature carried out among workers, which may constitute a selection bias. By including only civil servants, a group that may have better access to health care than the general population, this cohort adds another selection bias. On the other hand, because women had to remember the age of menopause, there may be some inaccuracies in the data because they refer to events that occurred in the past. Furthermore, no medical or surgical therapies were evaluated during follow-up that could have modified the life expectancy of these women. Finally, it is impossible to fully adjust lifestyle factors, such as diet, smoking, alcohol consumption and physical activity, factors that influence the age of menopause and mortality, therefore, the observed results may be due to partially to residual confounding by unmeasured lifestyle and related socioeconomic factors.

The strengths of our study, it is worth mentioning its longitudinal cohort design that evaluated the impact of baseline risk factors on mortality in a highly homogeneous middle-aged female population followed for three decades. For data collection, instead of sending a simple questionnaire to the subjects, trained nurses interviewed them directly, using standardized definitions for risk predictors and helped them answer the questionnaire, and also measured their height, weight and pressure. Blood pressure, minimizing the probable information bias due to self-report.

5. Conclusion

Although POI affects a small group of women, its effect on mortality is important. It is necessary to insist on the need for health authorities, healthcare providers and the general population to implement measures to reduce this risk.

Contributors

Juan E. Blümel contributed to conception/design of the study, data collection, statistical analysis, initial drafting, and revision of the initial draft.

Edward Mezones-Holguín contributed to statistical analysis and revision of the initial draft.

Peter Chedraui contributed to initial drafting and revision of the initial draft.

Percy Soto-Becerra contributed to statistical analysis, initial drafting, and revision of the initial draft.

Eugenio Arteaga contributed to initial drafting, and revision of the initial draft.

María S. Vallejo contributed to initial drafting and revision of the initial draft.

All authors approved the final version of the manuscript.

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Ethical approval

The study was approved by the local ethics committee (Southern Metropolitan Health Service, Santiago de Chile, Chile. Memorandum N° 1:155/2918. April 20, 2018) and was in complete agreement with the Declaration of Helsinki. All women provided written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interest.

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