

Age at natural menopause and physical functioning in postmenopausal women: the Canadian Longitudinal Study on Aging

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Abstract

Objective: The aim of this study was to evaluate the association between categories of age at natural menopause (ANM) and gait speed (slowness) and grip strength (weakness), common measures of physical functioning in older women.

Methods: We analyzed data from the Canadian Longitudinal Study on Aging, which included participants from seven cities across Canada collected in 2012. The sample was restricted to women who reported to have entered menopause (N = 9,920). Women who had a hysterectomy before menopause were excluded since the age at which this surgical procedure was performed was not available. ANM was categorized into five groups: less than 40 (premature), 40 to 44 (early), 45 to 49, 50 to 54, and more than 54. We conducted linear regressions to assess the association between ANM and gait speed (m/s) and grip strength (kg) adjusting for participant age, education, body mass index, smoking, use of hormone therapy, height, and province of residence.

Results: Mean ANM was 49.8 (95% confidence interval [CI]: 49.7-50.0), with 3.8% of women having a premature menopause; the average gait speed was 0.98 m/s (standard deviation: 0.22), the average grip strength was 26.6 kg (standard deviation: 6.39). Compared to women with ANM of 50 to 54, women with premature menopause had 0.054 m/s (95% CI -0.083, -0.026) lower gait speed when adjusting for age and study site. In the fully adjusted model, the association was attenuated, 0.032 m/s (95% CI -0.060, -0.004). ANM was not associated with grip strength.

Conclusion: Our study suggests that premature menopause (<40 years) may be associated with lower gait speed (slowness) among Canadian women. No association was observed between ANM and grip strength. Future studies should include a life course approach to evaluate whether social and biological pathways modify the association between age at menopause and physical function in populations from different contexts.

Key Words: Menopause – Physical functioning – Premature menopause – Women’s health.

Among older adults, women experience worse physical function and greater physical decline than men at similar ages.¹⁻⁵ In addition to known social inequalities between men and women,⁶ biological factors may contribute to this sex difference in functional outcomes. Menopause is

associated with estrogen decline, and earlier ages at menopause entail longer exposure to the potentially adverse consequences of this decline, including osteoporosis⁷ and cardiovascular disease,⁸ both of which contribute to physical function decline.^{9,10} Although the effect of age at menopause on bone density loss

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is well recognized,¹¹ its effect on skeletal muscle mass and strength has been less studied.^{12,13}

Aging is associated with a loss of muscle mass and strength that results in physical functioning decline,^{14,15} disability,¹⁶ falls,¹⁷ and mortality.¹⁸ Grip strength and gait speed are common biometric measures of physical functioning.¹⁹ They are also established indicators of sarcopenia and frailty, which are major contributors of poor health, disability, and premature death. Among postmenopausal women, only three studies conducted in the United States have examined the association between age at menopause, type of menopause and gait speed, or grip strength, and these studies observe better physical function among women who transition naturally to menopause at later ages.²⁰⁻²² In a multicity sample of 775 women aged 65 to 74 years from Albania, Brazil, Colombia, and Canada (the IMIAS—International Mobility in Aging Study), we recently reported that, all sites combined, women with age at natural menopause (ANM) 55 or more had higher gait speed than those with ANM 50 to 54. Women with premature menopause (<40 years) had significantly lower grip strength compared with women with later ANM. In region-specific analyses, ANM was associated with grip strength in Albania and Latin America and with gait speed in Albania only. No associations were observed in Canada.^{23,24}

The objective of the present study was to examine the association between categories of ANM and physical functioning in a nationally representative sample from Canada (the Canadian Longitudinal Study on Aging [CLSA]). Our hypothesis is that women who experience menopause at later ages would perform better in physical performance tests (ie, grip strength and gait speed) than would women who experience menopause at earlier ages.

METHODS

Study sample

The CLSA is a national cohort study of adults aged 45 to 85 years of age at recruitment and followed for at least 20 years or until death. Slightly more than 50,000 men and women across Canada's 10 provinces were recruited at baseline between 2010 and 2013. A total of 21,241 individuals participated in a telephone interview (tracking cohort) and 30,111 individuals participated in an in-home interview (comprehensive cohort). In the present study, we used baseline data from about 15,320 women who participated in the in-home interviews conducted in seven provinces: Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Nova Scotia, Ontario, and Quebec. Details about CLSA design, recruitment, and study procedures have been described elsewhere.²⁵

Outcome measures

Gait speed was measured using the timed 4-m walk test. To this end, an area of floor was marked to specify the distance in meters and participants were asked to stand just behind the start line and to start walking right after the command "Ready, Set, Go." Site staff started the stopwatch right after speaking the command and stopped it as soon as the participant crossed the finish line. From this assessment, gait speed

(in m/s) was calculated by dividing the time that it took a participant to cross the finish line by 4 m (time/meters). Participants were excluded from participation if they were unable to stand unassisted and/or unable to walk unassisted by another person.²⁶

Handgrip strength was measured in kilograms using the Tracker Freedom Wireless Grip Dynamometer. Handgrip of the dominant hand was measured unless there was a contraindication. Contraindications for testing were defined as follows: surgery on hand or wrist within the last 3 months; pain or paralyses in hand or wrist due to arthritis; tendinitis; carpal tunnel syndrome; open sores or bruising on hand; cast on hand or arm, prosthetic arm, hand, or fingers. If testing was contraindicated for both hands, the person was excluded from the test.

Exposure variable

Women were asked whether they had gone through menopause (defined as "menstrual periods stopped for at least 1 year and did not restart") and at what age. Hysterectomy was a response option for women who underwent hysterectomy before natural menopause occurred. Age at hysterectomy was, however, not recorded, or if oophorectomy was performed at the time of hysterectomy. In women who indicated having gone through natural menopause, but for whom an age at menopause was missing, we substituted reported age at start of hormone therapy (HT) if available ($n = 73$). ANM was categorized into five groups: less than 40 (premature), 40 to 44 (early), 45 to 49, 50 to 54, and more than 54. The age group 50 to 54 was set as the reference group since it represents the median ANM in women from CLSA (51 years).²⁷

Covariates

We selected covariates based on previous literature indicating these variables as important predictors of the study outcomes.²⁸⁻³⁰ Education was self-reported and categorized based on the highest level of education completed: primary completed or less, secondary completed, postsecondary completed. The interviewer following a standard protocol measured height and weight, and the body mass index (BMI) was calculated in kg/m^2 . BMI of less than 18.5 was categorized as underweight, BMI of 18.5 to 24.9 as normal weight, BMI of 25.0 to 29.9 as overweight, and BMI of 30 or more as obese. The use of HT was self-reported and dichotomized into those who had ever used HT and those who had never used HT. Smoking status was self-reported and dichotomized as current smokers and nonsmokers (including former smokers). Age was calculated by deducting the date of birth from the date of interview. The interviewer recorded the study site.

Statistical analyses

Sample characteristics were compared across categories of ANM. The crude and multivariate associations between covariates, gait speed, and grip strength were assessed using linear regression. An age-squared parameter was added in all regressions to better describe the increase in poor physical performance, as women get older. This is especially true when women

younger than 65 years are included in the analyses. Bonferroni adjusted *P* values were calculated in pairwise comparisons across categories of ANM. Multivariate regression analyses were conducted with adjustment for age, age*age, and site; and then by all covariates. We applied sampling weights (strata and analytic sampling weight) as per CLSA manual to account for the sampling methods. Analysis was conducted using Stata, version 14.

RESULTS

Sample characteristics

In total, 5,320 women completed the CLSA in-home interview. After applying the exclusion criteria (Fig. 1), we included 9,718 women in the gait speed analysis, and 8,867 women in the grip strength analysis. Mean ANM was 49.8 (95% confidence interval: 49.7-50.0). Premature menopause was present in 3.8% of women and early menopause in 8.7%. Table 1 presents the differences in ANM according to covariates. Women from Newfoundland and Labrador had a higher proportion of premature menopause (6.2%), and a lower proportion ANM 54 or older (12.3%) compared to other provinces. Women with lower education had a higher proportion of earlier ANM. Underweight, overweight, and obesity were associated with earlier ANM compared to normal weight women. The use of HT was more prevalent in women with earlier ANM, and current smoking was associated with earlier ANM compared to nonsmokers.

Table 2 presents the results of the univariate analysis of gait speed and grip strength with covariates. The overall sample average gait speed was 0.97 m/s (standard deviation: 0.22), the average grip strength was 26.6 kg (standard deviation: 6.39). ANM was significantly associated with both gait speed and grip strength. Compared to the reference group of ANM

of 50 to 54, gait speed and grip strength were -0.07 m/s and -0.94 kg lower for women with an ANM of less than 40; and -0.02 m/s and -1.03 kg in women with ANM >54 . Compared to women in Alberta, women in British Columbia and Nova Scotia had faster gait speed, whereas women in Manitoba and Newfoundland and Labrador had slower gait speed. Women in Manitoba, Nova Scotia, Ontario, and Quebec all had lower grip strengths compared to women in Alberta. Younger participants and those with higher education levels all had higher gait speed, and higher grip strength compared to older participants and those with a lower education. Respondents who were taller had higher gait speed and grip strength. Respondents who were overweight or obese had lower gait speed compared to those with a normal weight. Conversely, respondents who were underweight had lower grip strength compared to those with normal weight. Women who had never used HT had higher gait speed and higher grip strength compared to those who ever used HT. Although smoking was not associated with gait speed, it was associated with a higher grip strength (Table 2).

Table 3 presents results of the multivariate models testing for an association between ANM and the two outcomes of interest. In model 1, adjusting for age and site, gait speed was 0.054 m/s lower for women with an ANM of less than 40 as compared to the reference group ($P < 0.001$). This is equivalent to 5.5% slower (difference divided by the mean in the 50-54: $0.054/0.98 \times 100 = 5.5\%$). This association is attenuated in the fully adjusted model with a difference of 0.032 m/s ($P = 0.016$). The difference between those who underwent menopause at 55+ and the reference group was no longer significant in the multivariate model. Low education, shorter height, being overweight or obese, and smoking were related to lower gait speed (Fig. 2). None of the multivariate models

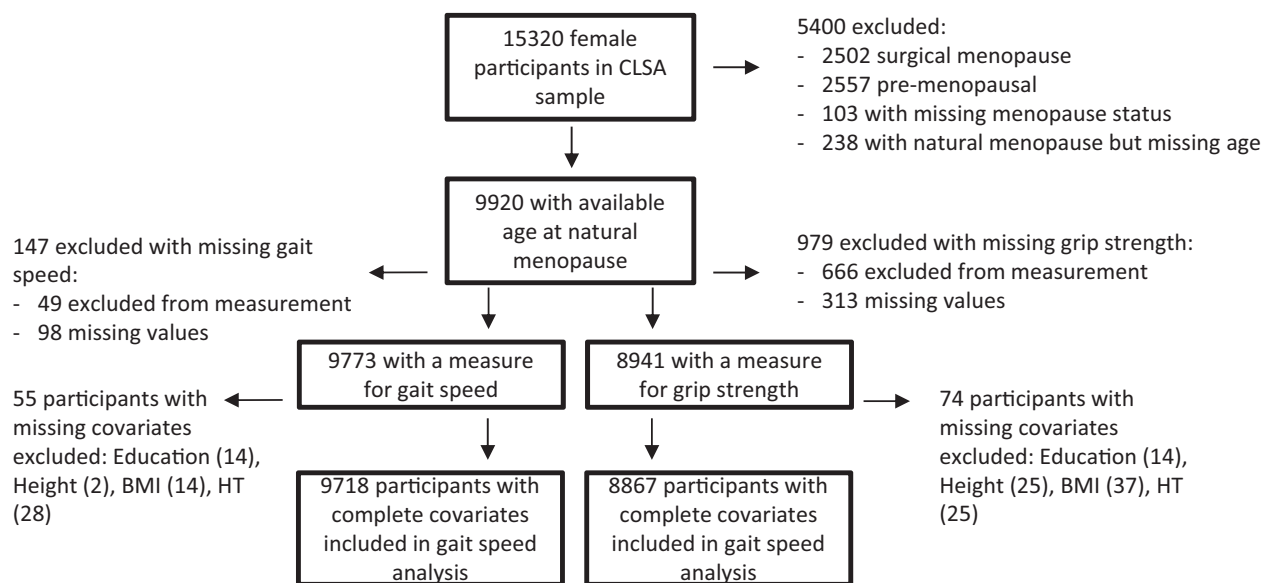


FIG. 1. Flow diagram of participant inclusion for gait speed and grip strength analysis. BMI, body mass index; CLSA, Canadian Longitudinal Study on Aging; HT, hormone therapy.

TABLE 1. Distribution/means of sample characteristics by age at menopause

Characteristics	Age at menopause—categories				
	<40 (N = 366)	40-44 (N = 830)	45-49 (N = 2,311)	50-54 (N = 4,623)	>54 (N = 1,643)
Total	3.8%	8.7%	25.1%	47.2%	14.9%
Study site ^a					
Alberta	3.6%	8.0%	27.4%	46.5%	14.3%
British Columbia	2.6%	8.1%	24.5%	49.8%	14.8%
Manitoba	3.9%	9.9%	27.1%	44.0%	15.0%
Newfoundland and Labrador	6.2%	9.0%	30.9%	41.4%	12.3%
Nova Scotia	1.8%	9.3%	23.9%	47.8%	17.0%
Ontario	3.2%	7.4%	23.4%	49.1%	16.7%
Quebec	5.4%	10.1%	23.9%	46.8%	13.6%
Age, mean (SE)	62.9 (0.56)	61.9 (0.38)	60.9 (0.22)	62.6 (0.14)	66.3 (0.19)
Education, highest level completed ^a					
Primary or illiterate	11.6%	12.1%	24.7%	37.9%	13.5%
Secondary	4.9%	9.9%	25.4%	43.7%	15.9%
Postsecondary	2.9%	8.2%	25.1%	48.8%	14.8%
Height, mean (SE)	159.9 (0.36)	161.3 (0.25)	161.9 (0.15)	161.6 (0.10)	161.1 (0.17)
BMI categories ^a					
Underweight	5.7%	12.0%	26.0%	45.2%	10.9%
Normal weight	2.7%	8.2%	26.2%	49.6%	13.1%
Overweight	3.6%	8.7%	24.8%	46.7%	15.9%
Obese	5.3%	9.3%	24.2%	44.9%	16.2%
HT, ever ^a					
Ever	6.0%	11.1%	24.8%	43.2%	14.8%
Never	2.4%	7.4%	25.5%	49.7%	14.9%
Smoking, last 15 years ^a					
No	3.3%	8.1%	24.5%	48.4%	15.5%
Yes	8.2%	16.0%	31.8%	35.4%	8.5%

BMI, body mass index; HT, hormone therapy.

^aDifferences across categories of age at menopause at covariate level are significant at $P < 0.0001$.

shows a significant association between ANM and grip strength (Table 3); being underweight remained related to lower grip strength in the final model, while being obese and overweight was related to higher grip strength (Fig. 2). Neither education, nor HT, nor smoking was related to grip strength in the final model.

DISCUSSION

Our study assessed the association of ANM with gait speed and grip strength in a national sample of postmenopausal women in Canada. Our results do not support our hypothesis that women who experience menopause at later ages would perform better in physical performance tests (ie, grip strength and gait speed) than would women who experience menopause at earlier ages. We, however, found that premature menopause (ANM before 40 years) was associated with 0.032 m/s less gait speed, a clinically relevant difference with important consequences for future health and quality of life for women.^{31,32} In women from The National Health and Nutrition Examination Survey, Tom et al²¹ reported a walking speed difference of 0.05 m/s slower between those who underwent menopause before 45 years old and those who experienced menopause at 50 to 54 years, with a mean age at interview of 70.6 years (10 years older than women in our study). In the case of grip strength, although in the univariate model premature menopause was associated with a lower grip strength, this association disappeared in the adjusted model. This finding is contrary to studies that have reported decline of grip strength with menopause status,^{33,34} but similar to

others that did not find association between menopause status, timing of menopause, and grip strength.^{35,36}

In a recent publication, premature and early menopause were related to greater risk of frailty, as defined by a non-weighted sum of accumulated health-related deficits (frailty index), in women from CLSA.³⁷ The fact that in our study the effect of premature menopause was related to gait speed independently of social and health variables may be explained by mechanisms through which low levels of estrogens affect physical function and muscle mass. It is possible that as a consequence of decreased estrogen levels, the respiratory and cardiovascular fitness is affected in women with premature menopause, and not only the musculoskeletal system. Increasing risk of earlier menopause has been observed among CLSA women with cardiovascular disease; although the direction of the association remains to be elucidated.²⁷ Premature menopause has been related to greater cardiovascular risk,³⁸ diabetes mellitus,³⁹ depression,⁴⁰ osteoporosis, and fracture risk,⁴¹ which could contribute to the associations between premature menopause and lower gait speed found in our study.

Factors associated with premature menopause (ANM < 40 years) are not completely understood. Known etiological factors are chromosomal abnormalities, fragile X syndrome, or autoimmune diseases (adrenal or ovarian antibodies). In 90% of the cases the etiology, however, remains unknown.⁴² Premature menopause could also be a marker of perinatal history, earlier social reproductive outcomes and adversities, and poor social and health conditions during adulthood. Using

TABLE 2. Linear univariate regression of gait speed and grip strength by sample characteristics

Characteristics	Gait speed			Grip strength		
	Difference	95% CI	P ^a	Difference	95% CI	P ^a
Age at menopause, categories						
Overall P value			<0.001			<0.001
<40	-0.07	-0.10; -0.04	<0.001	-0.94	-1.86; -0.02	0.042
40-44	-0.01	-0.03; 0.008	0.59	-0.030	-0.69; 0.63	1.00
45-49	-0.01	0.015; 0.01	1.00	0.07	-0.35; 0.50	1.00
50-54	Ref	Ref	Ref	Ref	Ref	Ref
>54	-0.02	-0.04; -0.01	0.001	-1.03	-1.48; -0.57	<0.001
Study site						
Overall P value			<0.001			<0.001
Alberta	Ref	Ref	Ref	Ref	Ref	Ref
British Columbia	0.05	0.03; 0.08	<0.001	-0.07	-0.79; 0.65	1.00
Manitoba	-0.03	-0.06; -0.007	0.004	-1.53	-2.29; -0.78	<0.001
Newfoundland and Labrador	-0.03	-0.06; -0.004	0.01	-0.01	-0.88; 0.86	1.00
Nova Scotia	0.10	0.06; 0.13	<0.001	-0.95	-1.80; -0.10	0.018
Ontario	-0.04	-0.02; 0.02	1.00	-0.93	-1.66; -1.97	0.0049
Quebec	0.012	-0.01; 0.03	1.00	-0.78	-1.48; -0.07	0.021
Age (each additional year)	-0.007	-0.007; -0.006	<0.001	-0.27	-0.28; -0.26	<0.001
Education						
Overall P value			<0.001			<0.001
Less than secondary	Ref	Ref	Ref	Ref	Ref	Ref
Secondary	0.08	0.05; 0.10	<0.001	2.04	1.34; 2.74	<0.001
Postsecondary	0.11	0.08; 0.13	<0.001	2.52	1.90; 3.14	<0.001
Height (each cm increase)	0.005	0.005-0.006	<0.001	0.39	0.37-0.41	<0.001
BMI						
Overall P value			<0.001			<0.001
Underweight	-0.070	0.13; -0.000	0.042	-3.7	-5.19; -2.42	<0.001
Normal weight	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	-0.037	-0.04; -0.024	<0.001	0.14	-0.24; 0.52	1.00
Obese	-0.10	-0.11; -0.09	<0.001	0.09	-0.31; 0.50	1.00
HT						
Ever	Ref	Ref	Ref	Ref	Ref	Ref
Never	0.01	0.006; 0.024	0.01	1.14	0.87; 1.41	<0.001
Smoking, currently						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	-0.016	-0.03; 0.00	0.06	0.72	0.23; 1.21	0.01

BMI, body mass index; CI, confidence interval; HT, hormone therapy.
^aOverall P was calculated using F statistics. Paired differences were calculated using t-test.

the CLSA, Costanian et al²⁷ found education to be an important social determinant of earlier menopause. Grip strength levels are related to poor social conditions in early life, including education and income.⁴³ This finding seems to be in support of an important relationship between social conditions and the timing of menopause as we have previously demonstrated,⁴⁴ and maybe the relationship between menopause and physical functioning. In relation to grip

strength, we have reported associations between menopause status and grip strength in Brazil,⁴⁵ and categories of ANM in Colombia, Brazil, and Albania, but no association was found in women from two cities in Canada.^{23,24} Similarly, timing of menopause was not related to grip strength in UK.³⁶ Additional studies comparing populations with diverse social exposures are needed to determine whether grip strength is a more sensitive indicator of earlier reproductive aging among

TABLE 3. Multivariate linear regression models presenting the association of age at natural menopause with gait speed and grip strength

ANM	Gait speed						Grip strength					
	Model 1: age and study site only ^a			Model 2: model 1 + all covariates ^b			Model 1: age and study site only ^a			Model 2: model 1 + all covariates ^b		
	Mean difference	95% CI		Mean difference	95% CI		Mean difference	95% CI		Mean difference	95% CI	
<40	-0.054	-0.083	-0.026	-0.032	-0.060	-0.004	-0.80	-1.63	0.03	-0.41	-1.19	0.36
40-44	-0.008	-0.027	0.010	0.000	-0.018	0.018	-0.014	-0.62	0.59	0.09	-0.45	0.64
45-49	-0.003	-0.016	0.010	-0.000	-0.013	0.012	-0.27	-0.67	0.11	-0.24	-0.60	0.11
50-54	Ref			Ref			Ref			Ref		
55+	-0.004	-0.019	0.010	-0.002	-0.016	0.012	-0.027	-0.45	0.39	-0.10	-0.49	0.28

ANM, age at natural menopause; CI, confidence interval.
^aModel 1: age, age square and site.
^bModel 2: model 1 plus education, height, body mass index (BMI), smoking, and hormone therapy (HT).

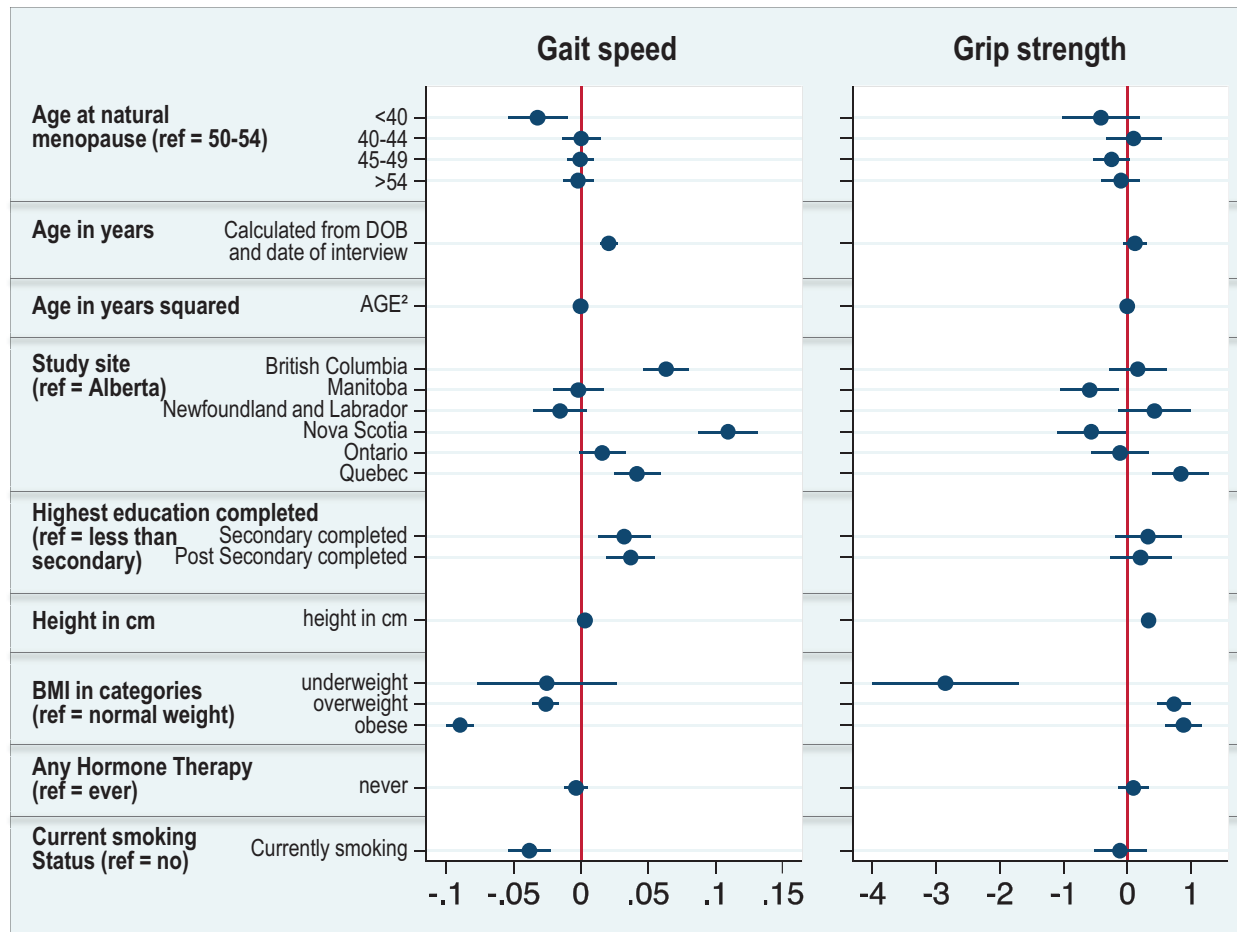


FIG. 2. Multivariate regression analysis for gait speed and grip strength by all covariates.

low socioeconomic populations than high-income ones, like Canada. Although CLSA has information about education as an indicator of socioeconomic conditions early in life, additional markers of childhood reproductive and social adversity are not available (ie, parental income, childhood violence, or abuse). As such, we were not able to account for those factors in our study, raising the possibility of residual confounding. In our recent International Mobility in Aging Study in women from Albania, Latin America, and Canada, the inclusion of childhood reproductive and social conditions in our model, however, did not change the associations between categories of ANM and measures of physical function.^{23,24}

In addition to residual confounding, it is important to highlight other limitations of our study. Women with an age at menopause of less than 40 were significantly more often excluded from performing the gait speed and grip strength test compared to women with an age at menopause 45 to 49, 50 to 54, or older than 54 (data not shown). Thus, missing information on premature menopausal women could be more related to inability to perform the test. This could have led to underestimation of our associations. The recent study using the frailty index as an outcome in the CLSA excluded women with a history of ovarian and breast cancer,

and even with that exclusion, premature menopause was related to the frailty index.³⁷ As a sensitivity analyses (data not shown), we also excluded women with these cancers, and our findings remained the same.

CLSA is a national sample of Canadian women; however, it does not represent more socially marginalized populations, such as immigrants and First Nations people; thus, its generalizability remains an issue. The report of age at menopause is consistent with other high-income countries⁴⁶; thus, we do not think there was misclassification of the exposure. We do not have age at hysterectomy nor information on if hysterectomy led to surgical menopause (oophorectomy). Women with hysterectomy were excluded; thus, our comparison remains among those with natural menopause. Women with a hysterectomy in the CLSA were more likely to be frail.²⁷ Further analysis of our data (not shown here) demonstrates that inclusion of hysterectomy as another menopause category did not change the direction nor significance of the associations reported here. In those analyses, women with a history of a hysterectomy had lower gait speed than women in the mean age of natural menopause, but no differences were found between women with a hysterectomy versus those with natural menopause at age 50 to 54 in grip strength.

CONCLUSIONS

Among women from the CLSA, we assessed the association of ANM with gait speed and grip strength. Premature menopause (<40 years) was associated with 0.032 m/s lower gait speed, but not with grip strength. Women with premature menopause should be considered as a clinical priority group for promotion of healthy aging initiatives that have been demonstrated to improve physical function, such as physical activity interventions⁴⁷ and nutritional supplementation.⁴⁸ Future studies should include early life social and reproductive exposures to evaluate if social and biological pathways modify the association between age at menopause and physical function in populations with different socioeconomic backgrounds.

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