Obesity and Lowered Cognitive Performance in a Canadian First Nations Population

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The association between obesity, other cardiovascular risk factors, and cognitive function in a Canadian First Nations population was investigated using a cross-sectional design. Eligible individuals were aged ≥18 years, without a history of stroke, nonpregnant, with First Nations status, and who had undergone cognitive function assessment by the Clock Drawing Test (CDT) and Trail Making Test Parts A and B. Parts A and B were combined into an Executive Function Score (TMT-exec). Hypertension, a previous history of cardiovascular disease, dyslipidemia, metabolic syndrome, insulin resistance, and the presence and duration of diabetes were examined in addition to obesity. In the case of TMT-exec only, obese individuals were at an approximately fourfold increased risk for lowered cognitive performance compared to those who were not obese in multivariable models (odds ratio (OR): 3.77, 95% confidence interval (CI): 1.46–9.72) whereas there was no effect for overweight individuals compared to those with a normal weight in unadjusted analysis. Those having an increased waist circumference also had 5 times the risk compared to those without an increased waist circumference (OR: 5.41, 95% CI: 1.83–15.99). Adjusted for age, sex, and insulin resistance, individuals having the metabolic syndrome were at an approximately fourfold increased risk compared to those without the metabolic syndrome (OR: 3.67, 95% CI: 1.34–10.07). No other cardiovascular risk factors were associated. Obesity and metabolic syndrome were associated with lowered cognitive performance. These results highlight the importance of studying the health effects of obesity beyond traditional disease endpoints, even in a relatively youthful population.

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INTRODUCTION

The rising prevalence of obesity is a major public health concern in most developed countries, and increasingly also in many developing countries and societies undergoing rapid social transitions, such as indigenous peoples (1). In addition to the well recognized adverse health effects of obesity (2), emerging evidence points to the fact that cognitive function is also compromised in the presence of obesity (3). Specifically, many studies demonstrate an increased risk of cognitive dysfunction or dementia in obese individuals (4–10). Complicating the understanding of a direct effect of obesity is the fact that underlying vascular and metabolic complications prevalent in obesity likely contribute indirectly in obese individuals as hypertension (11), hyperlipidemia (12–14), metabolic syndrome (15), insulin resistance (16–19), and diabetes (20) are all risk factors for both cognitive decline and dementia. Nevertheless, some studies continue to observe increased risk in obese individuals even after adjustment for these metabolic and vascular factors (8–10).

Current longer term prospective studies indicate that obesity in mid adulthood contributes to dementia risk in older age (8–10). These data are consistent with a life course approach, where midlife cerebrovascular damage may be evident in cognitive functions, such as executive function, but with persistent exposure to the neuropathological effects of being overweight or obese, cerebral damage is exacerbated, and progression to dementia occurs (21). This chronic model of early dysfunction with progression to dementia is especially disturbing given the increasing prevalence of early onset obesity in many populations.

Although many different cognitive domains are compromised in the presence of obesity (22), this study focused on executive function, as early deficits can be associated with progression to dementia, especially vascular dementia (23). The objective of this study was to examine the association between anthropometric, vascular, and metabolic risk factors and cognitive function in a Canadian First Nations population. A positive

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association between cardiovascular risk factors and lowered cognitive performance was hypothesized, with a gradient of increased risk according to the level of obesity, vascular, and metabolic dysfunction.

METHODS AND PROCEDURES

This is a cross-sectional study conducted in a road-accessible First Nations community in southern Manitoba, Canada. The study was approved by the Human Ethics Boards of the University of Manitoba and the University of Toronto, with the approval of, and in partnership with, the particular First Nations community. Eligible individuals were nonpregnant community residents, aged ≥18 years, without a history of stroke, and designated with First Nations status. Recruitment occurred through home visits to each home in the community without sampling and advertisements in the local Health Center newsletter. All eligible community members were invited to participate (24). Anthropometric, vascular, and metabolic data were collected as part of a larger cross-sectional study on diabetes and complications associated with diabetes. After exclusions, there were 510 eligible individuals. Cognitive function was assessed in the context of another study that examined vascular abnormalities and cognitive function. Three cognitive tests were administered by two graduate student, research assistants, at the research study site. Among individuals with risk factor data, there were 207 eligible individuals with Clock Drawing Test (CDT) scores and 190 eligible individuals who completed Trail Making Test Parts A and B.

The CDT involves individuals having to draw in the numbers of a clock face. According to the Watson scoring method, three clock numbers in a quadrant are considered correct. Errors in the first to third quadrants are assigned a score of one and errors in the fourth quadrant are assigned a score of four, for a maximum total score of seven (25). Scoring was performed by two raters. Individuals with a CDT score of ≥4 by one of two raters were classified as having lowered cognitive performance and categorized as cases, whereas individuals with a CDT score of <4 by both raters were classified as not having lowered cognitive performance and categorized as controls.

Trail Making Test Part A consists of 25 circles on a sheet of paper. Participants are asked to connect the circles as quickly as possible, beginning with one and continuing in ascending sequence. Time in seconds to test completion is recorded and a maximum of 90 s is applied to individuals who cannot complete the test. Trail Making Test Part B involves the subject having to draw a line alternating between numbers and letters in ascending sequence as quickly as possible. Time in seconds to test completion is recorded and a maximum of 300 s is applied to individuals who cannot complete the test (26). A derived score was calculated, which was then used to classify individuals. Alternative derived scores such as the difference: (B − A) and ratio: (B/A) have also been used in other studies. They attempt to isolate executive functioning related to Part B and account for processing speed related to Part A (27). We designated ((B − A)/A) the Trail Making Test Executive Function Score (TMT-exec) as it combines previous concepts and therefore may be more indicative of executive function. Individuals with TMT-exec ≥2.33 were classified as having lowered cognitive performance and categorized as cases, whereas individuals with TMT-exec <2.33 were classified as not having lowered cognitive performance and categorized as controls. The cut point was determined from preliminary analysis in which the distribution of TMT-exec was bimodal (data not shown).

Information on risk factors was ascertained through clinical examination and in-person questionnaires administered by trained personnel. Hypertension was defined as systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg (28). Self-report of at least one of the following was used to define a previous history of cardiovascular disease: angina, history of angioplasty or revascularization, myocardial infarction, and peripheral arterial disease. Fasting venous blood samples were collected, stored at −20°C, and analyzed for triglycerides, high-density lipoprotein, glucose, and insulin. Weight and height were collected and used to calculate the BMI. Individuals were classified in four categories: underweight, BMI < 18.5 kg/m^2; normal weight, BMI: 18.5–24.9 kg/m^2; overweight, BMI: 25.0–29.9 kg/m^2; and obese, BMI ≥30.0 kg/m^2 (29). Waist circumference to the nearest 0.5 cm was determined at the level of noticeable waist narrowing using an inelastic tape measure. For individuals in whom waist narrowing was difficult to identify, an indeterminate waist was approximated by taking the girth at the estimated lateral level of the 12th or lower floating rib. Metabolic syndrome was defined as ≥3 of the following: waist circumference >102 cm (male) or >88 cm (female), triglycerides ≥1.7 mmol/l, high-density lipoprotein <1.0 mmol/l (male) or <1.3 mmol/l (female), hypertension defined as systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, and fasting blood glucose ≥6.1 mmol/l (28). Having dyslipidemia and an increased waist circumference were determined according to the National Cholesterol Education Program criteria (28). Insulin resistance was examined by the homeostasis model of assessment (30), and previously diagnosed diabetes and duration of diabetes were determined by self-report.

The proportion of individuals classified as cases and controls and who had complete information for cardiovascular risk factors were examined. Incomplete data for continuous cardiovascular risk factors were assigned to the mean value from among the total eligible population (n = 510), except where the mean and median values were quite different, and then the median value was assigned. Descriptive statistics and risk estimates using this conservative approach for handling missing data were compared to the strategy of deleting individuals with incomplete information. The results were similar and the former was used for subsequent multivariable analysis. For categorical cardiovascular risk factors, individuals with incomplete data were assigned to the referent group. Unadjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated using logistic regression to examine the associations between categories of cardiovascular risk factors and cognitive function defined by the CDT and TMT-exec. Cardiovascular risk factors with corresponding standard criteria were designated into categories based on existing cut points, whereas continuous risk factors without standard criteria were categorized according to their median value. The median value was determined from among controls. Multivariable logistic regression models were used to examine the associations between cardiovascular risk factors including hypertension, history of cardiovascular disease, dyslipidemia, obesity, metabolic syndrome, insulin resistance, diabetes and duration of diabetes, and cognitive function defined by the CDT and TMT-exec, while accounting for confounding variables. Potential confounding variables included all cardiovascular risk factors in addition to self-report of ever having smoked (no/yes). Statistical models were built separately for each risk factor with age and sex considered in all models. Confounding variables were included in the final models if $P < 0.2$ and/or if they were identified in the literature as confounders. Diabetes and duration of diabetes were entered in separate models. When examining the effects of dyslipidemia, obesity, metabolic syndrome, and insulin resistance, those having diabetes or fasting plasma glucose levels ≥7 mmol/l (e.g., undiagnosed diabetes) were excluded. Multivariable models were used to estimate the adjusted ORs, 95% CIs, and P values for each cardiovascular risk factor, while controlling for confounding variables. All analyses were calculated in SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

For the CDT, 90 of 207 individuals were classified as cases (CDT(+): 43.5%), whereas 117 individuals were classified as controls (CDT(−): 56.5%). Incomplete information for age, hypertension, history of cardiovascular disease, dyslipidemia, diabetes, and smoking predominated among the cardiovascular risk factors and occurred equally often by CDT status (CDT(+), n = 22; CDT(−), n = 22). A comparison of risk factor values for continuous variables showed no group differences (data not shown, $P > 0.05$ for all), and for the 207 individuals, the median age was 39 years (range: 19–65 years). **Table 1** shows the unadjusted ORs. Females had a twofold increased risk for lowered

Table 1 Unadjusted ORs and 95% CIs for demographic and cardiovascular risk factors and lowered cognitive performance by the CDT ($n = 207$)

Covariates	CDT(+), $n = 90$ n	CDT(−), $n = 117$ n	OR (95% CI)
Age			
<35 years	21	37	1.00
35–44 years	48	46	1.84 (0.94–3.60)
45–54 years	15	25	1.06 (0.46–2.44)
55+ years	6	9	1.18 (0.37–3.76)
Sex			
Males	33	67	1.00
Females	57	50	**2.31 (1.32–4.07)**
Hypertension			
No	81	103	1.00
Yes	9	14	0.82 (0.34–1.98)
History of cardiovascular disease			
No	80	98	1.00
Yes	10	19	0.65 (0.28–1.47)
Dyslipidemia			
No	16	32	1.00
Yes	74	85	1.74 (0.89–3.42)
Waist circumference			
Low risk	23	37	1.00
High risk	67	80	1.35 (0.73–2.49)
BMI			
Normal	10	18	1.00
Overweight	24	29	1.49 (0.58–3.83)
Obese	56	70	1.44 (0.62–3.37)
Obese			
No	34	47	1.00
Yes	56	70	1.11 (0.63–1.94)
MetS			
No	41	65	1.00
Yes	49	52	1.49 (0.86–2.60)
No. MetS components			
0	5	14	1.00
1	15	27	1.56 (0.47–5.17)
2	21	24	2.45 (0.76–7.95)
3+	49	52	2.64 (0.88–7.87)
Insulin resistance			
<4.2 units	36	57	1.00
≥4.2 units	54	60	1.43 (0.82–2.49)
Ever smoked			
No	32	34	1.00
Yes	58	83	0.74 (0.41–1.34)
Ever diabetes			
No	69	90	1.00
Yes	21	27	1.01 (0.53–1.95)
Duration of diabetes			
Never	69	90	1.00
<7 years	13	13	1.30 (0.57–2.99)
≥7 years	8	14	0.75 (0.30–1.88)

CDT, Clock Drawing Test; CI, confidence interval; MetS, metabolic syndrome; OR, odds ratio.
Boldface value denotes $P = 0.0035$.

cognitive performance by the CDT compared to males (OR: 2.31, 95% CI: 1.32–4.07). No other risk factors were shown to be significantly associated with the CDT. Table 2 shows the multivariable adjusted ORs. All associations were not statistically significant. Covariates for duration of diabetes were similar to those for diabetes, with covariates shown for diabetes only.

For the TMT-exec, 72 of 190 individuals were classified as cases (TMT-exec(+): 37.9%), whereas 118 individuals were classified as controls (TMT-exec(−): 62.1%). Incomplete information for age, hypertension, history of cardiovascular disease, dyslipidemia, diabetes, and smoking predominated among the cardiovascular risk factors and for TMT-exec(−) (TMT-exec(+), $n = 12$; TMT-exec(−), $n = 29$). For continuous risk factor variables, TMT-exec(+) individuals had a higher median BMI (TMT-exec(+): 33.6, interquartile range (IQR): 8.5 vs. TMT-exec(−): 30.2 kg/m^2, IQR: 10.2, $P = 0.0015$) compared to TMT-exec(−) individuals. There were no individuals who were underweight (range, TMT-exec: 19.2–53.3 kg/m^2). Group differences were also observed for waist circumference (TMT-exec(+): 109.0, IQR: 20.0 vs. TMT-exec(−): 102.5 cm, IQR: 21.3, $P = 0.0016$) and systolic blood pressure (TMT-exec(+): 127.7, IQR: 20.0 vs. TMT-exec(−): 127.7, IQR: 10.0 mm Hg, $P = 0.0429$). No other continuous risk factors showed group differences, and for the 190 individuals, the median age was 38 years (range: 19–62 years). Examining cardiovascular risk factors across tertiles for Trail Making Test-A showed no differences for all continuous variables, except age and systolic blood pressure ($P < 0.05$). Table 3 shows the unadjusted ORs. Individuals categorized as having an increased waist circumference were more likely to demonstrate lowered cognitive performance by TMT-exec compared to those without an increased waist circumference (OR: 2.97, 95% CI: 1.44–6.13). Individuals classified as obese (OR: 3.02, 95% CI: 1.57–5.81), and having metabolic syndrome (OR: 2.58, 95% CI: 1.41–4.73) were more likely to have lowered cognitive performance by TMT-exec compared to those who were not obese and who did not have the metabolic syndrome. When those who were overweight were removed from the referent group, the effect on lowered cognitive performance

Table 2 Multivariable adjusted ORs and 95% CIs for cardiovascular risk factors and lowered cognitive performance by the Clock Drawing Test

	Total population, *n* = 207	
	OR (95% CI)	*P* value
Model 1		
Age[a]	1.02 (0.99–1.05)	0.3422
Sex	2.52 (1.40–4.53)	0.0020
Hypertension	0.80 (0.31–2.09)	0.6513
CVD[b]	0.57 (0.24–1.38)	0.2126
Obese	0.97 (0.53–1.76)	0.9117
Ever smoked	0.71 (0.38–1.33)	0.2867
Model 2		
Age	1.01 (0.98–1.04)	0.3773
Sex	2.42 (1.37–4.28)	0.0024
CVD	0.54 (0.23–1.29)	0.1662
Model 3		
Age	1.01 (0.98–1.04)	0.4281
Sex	2.42 (1.37–4.28)	0.0024
CVD	0.54 (0.22–1.29)	0.1659
Diabetes	1.05 (0.51–2.19)	0.8873
Duration of diabetes[c]		
<7 years	1.47 (0.60–3.60)	0.3981
≥7 years	0.67 (0.24–1.88)	0.4444
	Among those without diabetes, *n* = 142	
	OR (95% CI)	***P* value**
Model 4		
Age	1.03 (0.99–1.08)	0.1541
Sex	3.62 (1.64–8.03)	0.0015
Hypertension	2.03 (0.38–10.76)	0.4038
CVD	0.16 (0.03–0.84)	0.0304
Dyslipidemia	2.09 (0.78–5.60)	0.1408
Obese	0.55 (0.21–1.41)	0.2119
Insulin resistance	2.13 (0.82–5.59)	0.1225
Ever smoked	0.80 (0.33–1.92)	0.6180
Model 5		
Age	1.03 (0.99–1.07)	0.1317
Sex	3.19 (1.48–6.86)	0.0031
CVD	0.15 (0.03–0.78)	0.0239
MetS	1.49 (0.61–3.59)	0.3801
Insulin resistance	1.57 (0.69–3.56)	0.2842
Model 6		
Age	1.03 (0.99–1.07)	0.1544
Sex	3.06 (1.40–6.69)	0.0051
CVD	0.16 (0.03–0.80)	0.0256
No. MetS components		
1	1.03 (0.27–3.91)	0.9626
2	1.31 (0.34–5.10)	0.6984
3+	1.77 (0.40–7.80)	0.4481
Insulin resistance	1.45 (0.60–3.50)	0.4129

CI, confidence interval; MetS, metabolic syndrome; OR, odds ratio.
[a]All variables are categorized as specified in **Table 1**, except for age, which is a continuous variable in years. [b]CVD, history of cardiovascular disease. [c]Duration of diabetes was entered in model 3 separately from diabetes. Never having diabetes is the referent group. Covariates not shown.

by TMT-exec for obesity increased and remained statistically significant (OR: 3.79, 95% CI: 1.34–10.73) compared to those with a normal weight. There was no effect for individuals categorized as overweight compared to those with a normal weight. When individuals categorized as having one or two components of the metabolic syndrome were removed from the referent group, those classified with ≥3 components of the metabolic syndrome were at an approximately 4.5-fold increased risk for lowered cognitive performance by TMT-exec (OR: 4.47, 95% CI: 1.21–16.59), compared to those with zero components. The unadjusted ORs for all other risk factors were not statistically significant. **Table 4** shows the multivariable adjusted ORs. Among individuals without diabetes, being obese was associated with an approximately fourfold increased risk for lowered cognitive performance by TMT-exec compared to those who were not obese (OR: 3.77, 95% CI: 1.46–9.72, $P = 0.0061$). When individuals categorized with an increased waist circumference were substituted for those who were classified as obese, and waist circumference was examined in the same multivariable model, there was a fivefold increased risk for lowered cognitive performance by TMT-exec compared to those without an increased waist circumference (OR: 5.41, 95% CI: 1.83–15.99, $P = 0.0023$). Metabolic syndrome was the only other cardiovascular risk factor found to be associated with TMT-exec (OR: 3.67, 95% CI: 1.34–10.07, $P = 0.0115$). Categorizing individuals with an increasing number of components for the metabolic syndrome showed that when those with one or two components were removed from the referent group, there was an 8.5-fold increased risk for those classified with ≥3 components compared to those with zero components, however the CI was wide (OR: 8.49, 95% CI: 1.57–45.86, $P = 0.0129$).

In stratified analysis, an interaction effect for age and obesity and age and waist circumference were examined. Among those without diabetes, a statistically significant increased risk for lowered cognitive performance by TMT-exec was shown for the younger age groups (<39 years), a magnitude of effect that was slightly higher than for the older age groups (≥39 years) for both obesity and waist circumference. However, we were unable to find a significant interaction term due to inadequate power.

DISCUSSION

Our study found that obesity, expressed as BMI or as a component of the metabolic syndrome was associated with

Table 3 Unadjusted ORs and 95% CIs for demographic and cardiovascular risk factors and lowered cognitive performance by the Trail Making Test Executive Function Score (TMT-exec) (*n* = 190)

Covariates	TMT-exec(+), *n* = 72 *n*	TMT-exec(–), *n* = 118 *n*	OR (95% CI)
Age			
<35 years	22	33	1.00
35–44 years	29	59	0.74 (0.37–1.48)
45–54 years	16	19	1.26 (0.54–2.97)
55+ years	5	7	1.07 (0.30–3.81)
Sex			
Males	27	61	1.00
Females	45	57	1.78 (0.98–3.24)
Hypertension			
No	61	110	1.00
Yes	11	8	2.48 (0.95–6.49)
History of cardiovascular disease			
No	60	103	1.00
Yes	12	15	1.37 (0.60–3.13)
Dyslipidemia			
No	13	30	1.00
Yes	59	88	1.55 (0.75–3.21)
Waist circumference			
Low risk	12	44	1.00
High risk	60	74	**2.97 (1.44–6.13)**
BMI			
Normal	5	21	1.00
Overweight	12	36	1.40 (0.43–4.53)
Obese	55	61	**3.79 (1.34–10.73)**
Obese			
No	17	57	1.00
Yes	55	61	**3.02 (1.57–5.81)**
MetS			
No	26	70	1.00
Yes	46	48	**2.58 (1.41–4.73)**
No. MetS components			
0	3	14	1.00
1	10	29	1.61 (0.38–6.79)
2	13	27	2.25 (0.55–9.22)
3+	46	48	**4.47 (1.21–16.59)**
Insulin resistance			
<4.4 units	29	59	1.00
≥4.4 units	43	59	1.48 (0.82–2.68)
Ever smoked			
No	22	40	1.00
Yes	50	78	1.17 (0.62–2.19)
Ever diabetes			
No	53	95	1.00
Yes	19	23	1.48 (0.74–2.97)
Duration of diabetes			
Never	53	95	1.00
<7 years	10	12	1.49 (0.61–3.69)
≥7 years	9	11	1.47 (0.57–3.77)

CI, confidence interval; MetS, metabolic syndrome; OR, odds ratio.
Significant values are denotes in bold face.

lowered cognitive performance of an executive origin. The pervasiveness of the obesity epidemic and its link to early onset decreases in cognitive function among a youthful First Nations population is a reason for concern.

This is the first study to show an association between obesity and lowered cognitive performance of an executive origin. Heterogeneous study designs limit a direct comparison of our results to previous studies. Studies that included global measures of cognitive function were mixed, with no association for obesity in a recent meta-analysis (3). Similarly, in our study, no effect for obesity was shown with the CDT. Our results would have been strengthened had we observed similar results for both the cognitive tests; however, it was expected given a moderate agreement between the two tests for case-control cross-classification. Previous studies have shown approximately two- to fivefold increased risks for midlife obesity measured by BMI (8–10) or waist circumference (4) and risk of dementia. Other studies supporting the association did not include fully adjusted analysis (5,7) or examined changes in cognitive performance (6). Metabolic syndrome was also associated, and it appears that the increased risk largely operated through obesity.

The underlying biological mechanism leading to lowered cognitive performance of an executive origin is not clear. The contribution of atherosclerosis to silent infarcts (31) and the role of inflammatory factors such as adipocytokines or adipokines produced by abdominal visceral fat to the progression of endothelial dysfunction to atherosclerosis (32) are the possibilities. If midlife obesity represents cumulative exposure to altered hormonal, metabolic, and inflammatory states from birth to adult life that then predicts cognitive decline and dementia in late life (33), then similar risks observed in our study suggest the accelerated effects of an obesity milieu on lowered cognitive performance, given the youthfulness of the TMT-exec population. The lack of underweight individuals in our study did not allow us to examine the U-shaped phenomenon of both underweight and obese individuals and an increased risk of dementia, as shown in previous studies (3).

The absence of an effect for hypertension, a history of cardiovascular disease, and dyslipidemia, all linked to atherosclerosis

Table 4 Multivariable adjusted ORs and 95% CIs for cardiovascular risk factors and lowered cognitive performance by the Trail Making Test Executive Function Score

	Total population, *n* = 190	
	OR (95% CI)	*P* value
Model 1		
Age[a]	1.00 (0.97–1.04)	0.8760
Sex	1.69 (0.89–3.22)	0.1101
Hypertension	2.46 (0.85–7.13)	0.0964
CVD[b]	1.27 (0.52–3.14)	0.6008
Obese	3.05 (1.43–6.52)	0.0039
Insulin resistance	0.73 (0.35–1.51)	0.3939
Ever smoked	0.99 (0.50–1.96)	0.9774
Model 2		
Age	1.00 (0.97–1.03)	0.9688
Sex	1.73 (0.91–3.28)	0.0958
Hypertension	2.39 (0.84–6.81)	0.1035
CVD	1.20 (0.49–2.95)	0.6932
Obese	3.11 (1.45–6.63)	0.0034
Diabetes	1.37 (0.60–3.11)	0.4538
Insulin resistance	0.68 (0.32–1.44)	0.3068
Duration of diabetes[c]		
<7 years	1.60 (0.57–4.43)	0.3703
≥7 years	1.14 (0.38–3.43)	0.8179
	Among those without diabetes, *n* = 132	
	OR (95% CI)	***P* value**
Model 3		
Age	1.02 (0.97–1.06)	0.4926
Sex	1.99 (0.87–4.56)	0.1027
Hypertension	3.50 (0.52–23.58)	0.1975
CVD	1.24 (0.30–5.05)	0.7648
Dyslipidemia	1.32 (0.46–3.80)	0.6119
Obese	3.77 (1.46–9.72)	0.0061
Insulin resistance	0.52 (0.20–1.39)	0.1913
Ever smoked	0.79 (0.32–1.99)	0.6209
Model 4		
Age	1.02 (0.98–1.06)	0.4219
Sex	1.47 (0.66–3.26)	0.3438
MetS	3.67 (1.34–10.07)	0.0115
Insulin resistance	0.61 (0.23–1.61)	0.3155
Model 5		
Age	1.01 (0.97–1.06)	0.5355
Sex	1.29 (0.56–2.93)	0.5489
No. MetS components		
1	1.13 (0.24–5.20)	0.8785
2	3.32 (0.74–14.91)	0.1178
3+	8.49 (1.57–45.86)	0.0129
Insulin resistance	0.42 (0.15–1.19)	0.1024

CI, confidence interval; MetS, metabolic syndrome; OR, odds ratio.
[a]All variables are categorized as specified in **Table 3**, except for age, which is a continuous variable in years. [b]CVD, history of cardiovascular disease. [c]Duration of diabetes was entered in model 2 separately from diabetes. Never having diabetes is the referent group. Covariates not shown.

(34) highlight the need to include more proximal risk factors. The increased risk for females in both unadjusted and multivariable models is not clear, though is likely as complex as the cardiovascular effects of sex steroids (35). The absence of an increased risk for diabetes and its metabolic counterpart insulin resistance is consistent with glucose dysfunctions, affecting cognitive tasks determined by the hippocampus (36), compared to those that are vascular sensitive.

This study has several limitations, including the absence of information on past history of traumatic brain injury (37) and other psychiatric (38) or depressive conditions (39) that may affect cognitive functioning. Use of prevalent cases in the study of obesity cannot rule out reverse causality (40); however, a number of prospective studies using dementia (8–10) as an end point would support forward directionality. The generalizability of the results is limited due to the volunteer nature of the population. Analysis of times to completion for Part A of the Trail Making Test with age was consistent with normative data (41), however times were shifted toward poorer performance. For the trails, the potential for malingering exists (42), whereas population-based estimates for the CDT does not exist.

In conclusion, this study showed an association between obesity, expressed as BMI or as a component of the metabolic syndrome and lowered cognitive performance in a First Nations population. The results highlight the importance of cognitive function assessment even in a relatively youthful population and the need to investigate the health effects of obesity beyond traditional disease end points but in intermediate states such as decreasing cognitive function.

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DISCLOSURE

The authors declared no conflict of interest.

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