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Physical activity and mortality in the general population with and without major depression

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Abstract

Background and aims: It is not yet well understood whether physical activity (PA) may protect against elevated mortality in major depression. Answering this question has implications for policy and practice. The aim of this study was to estimate the association of PA with mortality in major depressive disorder (MDD). Methods: We used data from the Canadian Community Health Survey—Mental Health and Well-Being (CCHS 2002), conducted in 2002 (n = 31,200), and the Canadian Community Health Survey—Mental Health (CCHS-MH 2012), conducted in 2012 (n = 20,935), for this analysis. Recreational PA was measured using metabolic equivalent of task (MET) values, classifying participants as active, moderately active, and physically inactive in the 2002 survey and as very active, active, moderately active, and physically inactive in the 2012 survey. Major depression was assessed using a fully structured diagnostic instrument, the Composite International Diagnostic Interview. Mortality data was obtained through data linkage. The analysis used Cox proportional hazard models to explore the associations. Results: PA in the 2002 survey was protective: HR 0.69 (95% CI 0.64–0.74) and HR 0.77 (95% CI 0.72–0.83) for the active and moderately active groups, respectively. In the 2012 survey, the HRs were 0.55 (95% CI 0.43–0.70), 0.57 (95% CI 0.43–0.75), and 0.59 (95% CI 0.46–0.76) for the very active, active, and moderately active groups, respectively. No interactions were significant. Conclusions: These results indicate that PA protects against elevated mortality to the same extent in those with MDD as in those without. These findings, which arise from a representative sample, support continued efforts to integrate PA into the management of depressive disorders at the population level.

Keywords: *depression*, *mortality*, *physical activity*, *protection*

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1. Introduction

Major depressive disorder (MDD) affects more than 300 million people worldwide, inducing a significant impact on social relationships and individual functionality. It is one of the leading causes of disability, incapacity, and elevated health-care cost [1, 2]. Moreover, many studies have reported elevated mortality rates in people experiencing mental disorders, including MDD [3–5].

It has been shown that patients with MDD have alterations in stress systems, including hypothalamic–pituitary–adrenal (HPA) axis function and increased levels of inflammatory biomarkers (CRP, IL-1, TNF-α, and IL-6) [6–9]. These factors may vary according to severity, duration of the disease, age, physical health conditions, and social factors [10, 11]. These changes are also associated with mortality [12–15].

An unhealthy lifestyle behavior, including physical inactivity, which is a common feature in depressed patients [16], may also contribute to elevated mortality [17–19]. On the other hand, physical activity (PA) improves physical health and may be protective against all-cause mortality [18, 20, 21].

Recent epidemiological studies have also emphasized the protective or beneficial effects of PA on incident depression [22, 23]. Pearce et al. [23] conducted a meta-analysis of the relationship between levels of PA and incident depression, concluding that 11% of depression cases could have been avoided if the population had been active at the level of current health recommendations. Another meta-analysis showed that the protective effects of PA against depression are observed regardless of age and sex and are significant across all geographical regions [24].

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Possible arguments for the protective effects of PA in MDD include its potential to improve social behavior and well-being [25, 26]; contribute to better regulation of the HPA axis [27]; decrease inflammation [27, 28]; contribute to the management of body mass index (BMI), including body fat loss and muscle mass gain [29]; and induce positive neuroplastic changes in brain structures related to mood [30].

While studies have established the protective effect of PA against depression, it is not known whether PA protects against elevated mortality in MDD. If so, this would provide an additional motivation for the implementation of practices and policies to increase PA in patients with depression. Such practices and policies would likely need to account for features of depression, such as diminished motivation and enjoyment of activities.

Only two cohort studies have investigated the relationship between PA and mortality in depression [31, 32]. Perez-Lasierra et al. evaluated mortality in National Health and Nutrition Examination Survey (NHANES) participants scoring 10 or above on the Patient Health Questionnaire – Brief (PHQ-9), a depressive symptom rating scale. However, they were unable to analyze the prevalence of MDD, as the PHQ-9 is a screening instrument rather than a diagnostic measure. Furthermore, they measured only two levels of PA and focused on adults aged 50 and older, whereas major depression is common in all age groups. The study by Liu and Jia [31] showed similar limitations, using a self-reported clinical diagnosis and PHQ-2 data from the UK Biobank. This study also covered a limited age range (37–73 years). They found a significant risk-elevating effect of lifetime MDD and a protective effect of PA. Multiplicative interactions between MDD and PA were not observed in their Cox proportional hazards model [31], but greater-than-additive interactions were observed.

For a better understanding of the effects of PA on mortality in major depression episode, it is necessary to have strong measures, a representative sample, and the ability to control for possible confounding variables. A particularly important confounder is age, as MDD often has its onset in late adolescence and early young adulthood [33], whereas mortality is strongly influenced by advancing age.

In this study, we used historical cross-sectional survey data that included administration of a validated, fully structured psychiatric diagnostic interview and an assessment of PA in a representative sample. These surveys were conducted in 2002 and 2012 and were later linked to a national mortality database. We hypothesized that PA would reduce the effect of major depression on elevated all-cause mortality.

2. Materials and methods

2.1. Data source: Canadian Community Health Survey 2002 and Canadian Community Health Survey 2012

The Canadian Community Health Survey—Mental Health and Well-Being (CCHS 2002) and the Canadian Community Health Survey—Mental Health (CCHS 2012) were cross-sectional mental health surveys based on nationally representative samples conducted by Canada's national statistical agency, Statistics Canada. These surveys collected data on demographics, health status, health determinants, and health-care utilization, with a strong focus on mental health. The target population was Canadian household residents aged 15 years and over living in any of the 10 provinces. Excluded were people living on "Indian" reserves and other aboriginal settlements, full-time members of the Canadian Armed Forces, and residents of institutions. For the CCHS 2002, the information was collected between May 2002 and December 2002, with a sample size of approximately (n = 31,200). For the CCHS 2012, data collection occurred between January 2, 2012, and December 31, 2012. A total of (n = 20,935). Please note that these numbers are rounded to the nearest five in keeping with Statistics Canada's data-release requirements for count data. Such rounding was not required for other types of estimates, such as frequencies and hazard ratios (HAs). Interviews were conducted using computer-assisted personal interviewing by trained and experienced interviewers. Statistics Canada calculates sampling weights that help ensure valid inference to the target (household) population, including adjustments for nonresponse. Exclusions from the sampling frame were similar to those in the 2002 survey: individuals living on "Indian" reserves and crown lands, health-care institution residents, full-time members of the Canadian Armed Forces, and residents of certain remote regions. In total, these exclusions amount to less than 3% of the population. Analyses of CCHS data do not require Ethics Review Board approval. Additional information on these surveys is available from Statistics Canada (https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=119789).

2.2. Physical activity measures

The PA module of the CCHS 2002 included items to assess recreational PA in the three months preceding the survey interview. The activities assessed by these items were "walking for exercise", "gardening or yard work", "swimming", "bicycling", "popular or social dance", "home exercises", "ice hockey", "ice skating", "in-line skating or rollerblading", "jogging or running", "golfing", "exercise class or aerobics", "downhill skiing or snowboarding", "bowling", "baseball or softball", "tennis", "weight training", "fishing", "volleyball", "basketball", and "other activities." Each activity is associated with an estimate of metabolic energy expenditure per hour of participation. While some of the listed activities do not represent vigorous PA, their associated low metabolic energy expenditures result in these activities making a small but accurate contribution to overall estimates of PA. The CCHS respondents are classified as active, moderately active, or inactive based on a PA index that estimates average daily PA over the past three months. The index is calculated as the sum of the average daily energy expenditure of all activities. Respondents are classified as follows: 3.0 kcal/kg/day or more = physically active; 1.5–2.9 kcal/kg/day = moderately active; less than 1.5 kcal/day = inactive [34]. We consider this classification to be consistent with current recommendations for 30–45 min of activity three to five times a week [35–38]. Activities that lead to an increase in daily energy expenditure of approximately 200–300 kcal/session can add up to 1,000–1,500 kcal/week (e.g., 3 kcal/kg/day in a 70 kg person leads to an expenditure of approximately 210 kcal/day). Physical activity with a frequency of five times a week can lead to a caloric expenditure equal to or greater than 1,050 kcal. This level of caloric expenditure is associated with substantial health benefits. Therefore, we decided to classify as "physically active" those who achieved more than 150 min/week, as well as those who achieved 30 min or more per day for more than three days per week. Based on these assumptions, we classified as "moderately active" those who have less than 150 min/week, expending

between 106 and 200 kcal/day. Caloric expenditures below 105 kcal were considered inactive, e.g., walking no more than 15 min everyday [39].

The PA module of the CCHS-MH 2012 also included items to assess recreational PA, indicating the average amount of time in hours that respondents reported doing moderate or vigorous PA in the past seven days. Response categories (reported in ranges) were converted to proportions of minutes, using average duration in hour units. We classified participants into four categories: very active physically (>300 min/week), active physically (150–300 min/week), moderately active (<150 min/week), and inactive physically (<15 min/week).

2.3. Major depressive disorder

The CCHS 2002 identified MDD in the past 12 months using a Canadian adaptation of the World Mental Health—Composite International Diagnostic Interview Instrument (WMH-CIDI) [40]. The WMH-CIDI is a lay-administered psychiatric interview based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). The CCHS-MH 2012 used the same interview. The experienced lay interviewers employed in the surveys were fully trained in administration of the WMH-CIDI. After administering the interview, a computerized algorithm was used to classify respondents as: (a) meeting the criteria for a lifetime major depressive episode (one or more episodes of major depression in their past life) and (b) meeting criteria for 12-month prevalence of MDD, based on having a major depressive episode in the 12 months prior to the interview. Due to concerns about the validity of lifetime prevalence ratings [41], past 12-month episodes were used in this analysis.

2.4. Demographic data (covariates)

Demographic data collected by both surveys included age, sex, marital status, and education. These variables were assessed using field-tested items developed by Statistics Canada. For marital status, we used four categories: married or common law, widowed, separated or divorced, and single (never married). Married or common law was used as the referent group in the analysis. Education referred to the highest level of education achieved by the respondent and was categorized into less than secondary school, secondary school graduate, and postsecondary, with postsecondary serving as the referent category.

2.5. Health outcomes (covariates)

2.5.1. Body mass index

The BMI is a quick and accurate method to determine health risk as it relates to body weight and height. BMI was measured in the 2002 and 2012 surveys, but in the 2002 survey, age restrictions resulted in the BMI being calculated only for a minority of the sample (n < 10,000). Exploratory analyses determined that BMI did not act as an effect modifying or confounding variable, so it is not reported in the analyses that follow.

2.5.2. Smoking

A potentially important confounding variable is smoking, which was not directly assessed in the CCHS 2002. However, the survey interview included an item asking whether respondents smoked more when they were stressed. We classified all respondents who answered affirmatively to this item as smokers. The CCHS-MH 2012 included a survey module to classify smoking status as never, former, or current.

2.5.3. Type of drinker

Type of drinker was assessed using field-tested items about drinking habits in both surveys, leading to the classification of respondents as regular, occasional, former, or never drinkers in 2012. In the CCHS-MH 2012, each respondent was classified as consuming alcohol on a regular, occasional, or never basis.

2.5.4. Chronic conditions

Both surveys asked respondents whether or not they had any long-term (>6 months) physical or mental health condition that had been diagnosed by a health professional. The chronic conditions included in this analysis were asthma, arthritis, back problems, high blood pressure, migraine, bronchitis, lung emphysema, diabetes, epilepsy, heart disease, cancer, stomach problems (e.g., ulcer), stroke, chronic disease, Alzheimer's disease, cataracts, glaucoma, and thyroid conditions.

2.5.5. Mortality

Data from the CCHS surveys was linked by Statistics Canada to the Canadian Vital Statistics Deaths database. Linkage procedures have been previously described and evaluated [42]. The linkage data from the CCHS 2002 (n = 5,635) was constructed as of June 2002, providing up to 15 years of follow-up time. The linkage data from the CCHS-MH 2012 (n = 1,175) is similarly available, providing up to five years of follow-up time. For respondents identified in the mortality database, the date of death was recorded, and time to death was calculated as the number of days between their survey interview date and the date of their death. Respondents who did not die were censored at the record linkage date.

2.6. Statistical analysis

Cox proportional hazard models were used in the analysis. We operationalized our hypothesis that PA would reduce the impact of major depression on all-cause mortality using interaction terms. The significance of the major depression by PA interaction term, assessed using a Wald test, served as a statistical test of whether PA modified the effect of major depression. Since these interactions were examined using a Cox proportional hazard model (HR), which is a log-transformed model, the interactions are assessed on the multiplicative scale.

Categorical variables were estimated as frequencies, using percentages (%) in descriptive tables. Continuous data is reported as means with 95% confidence intervals (CI). Covariates selected for this analysis, as listed above, have been previously reported to be determinants of mortality and may therefore act as confounders of the association between MDD and PA. To explore the relationship between PA and major depression on subsequent mortality, we initially examined interaction terms between these variables. Next, the age- and sex-adjusted main effects were estimated. In the survey dataset, we adjusted for other covariates one at a time and in a multivariable model to assess their potential confounding and/or joint confounding role. All analyses were conducted in the Prairie Regional Data Centre at the University of Calgary Campus. All analyses reported, except the relative excess risk due to interaction (RERI) estimates, used a recommended bootstrap weighting procedure incorporating a set of 1,000 replicate bootstrap weights, ensuring accurate estimates of parameters, standard errors, and 95% CI while accounting for design effects (clustering and unequal selection probabilities). **Tables 1** and **2** present all of the variables included in the analysis and specify

the choice of reference group for each variable. We also calculated the interaction on an additive scale to measure RERI, assuming that the Cox proportional hazard ratio minus one approximated relative excess risks. The RERI allows assessment of greater-than-additive interactions between two exposures. This parameter is used as an index for causal inference in epidemiology. If two exposures interact on a biological level, this is expected to manifest as a greater-than-additive interaction, quantified by the RERI, because the causal mechanisms that require both exposures mean that the joint exposure is associated with a higher risk than the sum of the individual exposures. Statistical analysis was performed in Stata v18 (StataCorp 2019), and statistical significance was assigned using $p < 0.05$.

Table 1 • Description of the CCHS 2002 sample

	Overall % (95% CI) *n* = 31,120[a]	**No major depression % (95% CI) *n* = 29,350[a]**	**Major depression % (95% CI) *n* = 1,625[a]**
Depression		95.3 (94.9–95.6)	4.7 (4.4–5.1)
Sex			
Male	50.8 (50.5–51.2)	96.4 (95.9–96.8)	3.6 (3.1–4.0)
Female	49.2 (48.8–49.5)	94.2 (93.6–94.7)	5.8 (5.2–6.3)
Age			
15–29	23.8 (23.1–24.5)	94.0 (93.3–94.8)	6.0 (5.2–6.7)
30–39	19.3 (18.6–19.9)	94.6 (93.9–95.4)	5.4 (4.6–6.1)
40–49	20.9 (20.1–21.6)	94.6 (93.6–95.6)	5.4 (4.4–6.4)
50–59	15.4 (14.8–16.1)	95.7 (94.9–96.4)	4.3 (3.6–5.1)
60 and above	20.6 (20.0–21.2)	97.6 (97.1–98.2)	2.4 (1.8–2.9)
Marital status			
Married	62.0 (61.3–62.8)	96.7 (96.3–97.1)	3.3 (2.9–3.7)
Divorced	12.8 (12.4–13.3)	92.0 (91.0–93.0)	8.0 (7.0–9.0)
Single	25.1 (24.4–25.8)	93.4 (92.6–94.2)	6.6 (5.8–7.4)
Education			
Less secondary	25.7 (25.0–26.5)	95.1 (94.4–95.7)	4.9 (4.3–5.5)
Second school	18.8 (18.1–19.5)	95.2 (94.5–95.9)	4.8 (4.1–5.5)
Some postsecondary	8.7 (8.2–9.1)	94.3 (93.2–95.5)	5.7 (4.5–6.8)
Postsecondary	46.8 (46.0–47.6)	95.6 (95.0–96.1)	4.4 (3.9–5.0)
Chronic condition			
None	29.2 (28.4–30.0)	97.5 (97.1–98.0)	2.5 (2.0–2.9)
One or more	70.8 (70.0–71.6)	94.3 (93.9–94.8)	5.7 (5.2–6.1)
Type of drinker			
Regular	58.1 (57.3–58.9)	95.5 (95.0–95.9)	4.5 (4.1–5.0)
Occasional	19.3 (18.7–19.9)	94.8 (94.0–95.6)	5.2 (4.4–6.0)
Former	13.0 (12.5–13.6)	94.0 (93.1–94.9)	6.0 (5.1–6.9)
Never	9.6 (9.1–10.1)	96.6 (95.5–97.7)	3.4 (2.3–4.5)
Physical activity			
Inactive	47.1 (46.2–47.9)	94.8 (94.3–95.4)	5.2 (4.6–5.7)
Moderate	26.8 (26.0–27.5)	95.5 (94.9–96.2)	4.5 (3.8–5.1)
Active	26.2 (25.4–26.9)	95.8 (95.2–96.3)	4.2 (3.7–4.8)
Smoker			
No	50.8 (50.5–51.2)	96.6 (96.2–96.9)	3.4 (3.1–3.8)
Yes	49.2 (48.8–49.5)	92.3 (91.5–93.1)	7.7 (6.9–8.5)
Mortality within 17 years of follow-up	–	13.0%	10.1%

[a]These counts are rounded to the nearest five in keeping with Statistics Canada data-release guidelines.

Table 2 • Description of the CCHS-MH 2012 sample

	Overall (n = 20,935)	Major depression (no) (n = 19,705[a])	Major depression (yes) (n = 1,125[a])
Depression		95.3 (94.9–95.8)	4.7 (4.2–5.1)
Sex			
Male	50.7 (49.5–51.9)	96.5 (95.8–97.2)	3.5 (3.0–4.1)
Female	49.3 (48.1–50.5)	94.2 (93.5–94.9)	5.8 (5.2–6.3)
Age (years)			
15–29	23.9 (22.9–24.9)	94.0 (93.0–95.0)	6.0 (5.0–7.0)
30–39	16.2 (15.3–17.0)	94.5 (93.0–96.0)	5.5 (4.0–7.0)
40–49	17.0 (15.9–18.0)	93.2 (91.8–94.6)	6.8 (5.4–8.2)
50–59	18.4 (17.4–19.5)	96.2 (95.5–96.9)	3.8 (3.1–4.5)
60 and above	24.6 (23.7–25.5)	97.9 (97.4–98.4)	2.1 (1.6–2.6)
Marital status			
Married	60.9 (59.7–62.0)	96.6 (96.1–97.1)	3.4 (2.9–3.9)
Divorced	12.5 (11.8–13.2)	93.2 (91.5–95.0)	6.8 (5.0–8.5)
Single	26.6 (25.6–27.7)	93.4 (92.5–94.3)	6.6 (5.7–7.5)
Education			
Less secondary	7.1 (6.7–7.6)	94.0 (92.2–95.8)	6.0 (4.2–7.8)
Second school	10.3 (9.7–11.0)	95.2 (93.9–96.4)	4.8 (3.6–6.1)
Some postsecondary	4.5 (3.9–5.1)	91.5 (88.5–94.5)	8.5 (5.5–11.5)
Postsecondary	78.0 (77.1–79.0)	95.7 (95.1–96.2)	4.3 (3.9–4.8)
Chronic condition			
None	26.7 (25.5–27.8)	97.5 (96.8–98.1)	2.5 (1.9–3.2)
One or more	73.3 (72.2–74.5)	94.5 (94.0–95.1)	5.5 (4.9–6.0)
Type of drinker			
Regular	59.3 (58.1–60.5)	95.8 (95.3–96.4)	4.2 (3.6–4.7)
Occasional	18.8 (17.8–19.8)	93.5 (92.4–94.6)	6.5 (5.4–7.6)
Never	21.9 (20.9–22.9)	95.7 (94.8–96.6)	4.3 (3.4–5.2)
Physical activity			
Very active	27.9 (26.8–29.1)	95.8 (95.0–96.6)	4.2 (3.4–5.0)
Active	17.6 (16.7–18.4)	96.5 (95.6–97.3)	3.5 (2.7–4.4)
Moderate active	27.9 (26.8–28.9)	94.6 (93.5–95.6)	5.4 (4.4–6.5)
Inactive	26.7 (25.6–27.7)	94.8 (94.0–95.6)	5.2 (4.4–6.0)
Smoker			
Nonsmoker	40.0 (38.8–41.2)	96.6 (95.9–97.3)	3.4 (2.7–4.1)
Current smoker	20.8 (19.8–21.8)	92.1 (90.9–93.2)	7.9 (6.8–9.1)
Former smoker	39.2 (38.1–40.4)	95.8 (95.1–96.4)	4.2 (3.6–4.9)
Mortality within 17 years of follow-up		4.1%	3.5%

[a]These counts are rounded to the nearest five in keeping with Statistics Canada data-release guidelines.

3. Results

3.1. Canadian Community Health Survey—Mental Health and Well-Being (2002)

The overall sample (n = 31,200) showed a prevalence proportion for past-year major depression of 4.7%. The prevalence was higher among those who were inactive (5.2%) than those who were moderately active (4.5%), and physically active (4.2%). In addition, past-year major depressive episodes were more prevalent in females (5.8%), younger individuals (15–29 years, 6.0%), divorced people (8.0%), participants with some postsecondary education but less than a university or college degree

(5.7%), underweight individuals (8.9%), former alcohol users (6.0%), and smokers (7.7%). More details are presented in **Table 1**. The frequency of deaths during follow-up (17 years) among those who were depressed was 13.0%, compared to 10.1% among those without major depression.

Initially, we estimated the HR for depression, adjusting for age and sex (HR = 1.74, p = 0.0001). When PA levels were added to the model along with their interaction terms, these interactions were not significant, indicating a lack of multiplicative interaction ($p > 0.05$). With the removal of the interaction terms, the HRs for PA indicated protective effects of being active (HR = 0.64, $p < 0.0001$) and being moderately active (HR = 0.71, p = 0.0001). In this model, the association of major depression with elevated mortality weakened slightly (HR = 1.66, $p < 0.0001$), as shown in **Table 3**.

Table 3 • Association of physical activity with major depression-associated mortality: Cox proportional hazard models based on the linkage of the CCHS 2002 to vital statistics data

CCHS 2002				
	HR	***Z***	***p* Value**	**LCI–UCI**
Model 1				
Major depression	1.74	7.65	<0.001	1.51–2.00
Male sex	1.53	15.71	<0.001	1.45–1.61
Age[a]	1.10	92.64	<0.001	1.10–1.10
Model 2				
Major depression	1.66	6.98	<0.001	1.44–1.91
Male sex	1.61	17.37	<0.001	1.52–1.70
Age[a]	1.10	91.75	<0.001	1.10–1.10
Inactive (ref)	–	–	–	–
Moderate	0.64	-11.9	<0.001	0.59–0.69
Active	0.71	-9.99	<0.001	0.66–0.76
Model 3				
Major depression	1.36	4.22	<0.001	1.18–1.58
Male sex	1.77	19.08	<0.001	1.67–1.88
Age[a]	1.10	79.93	<0.001	1.09–1.10
Marital status				
Single	1.55	9.18	<0.001	1.41–1.71
Divorced	1.30	8.44	<0.001	1.22–1.38
Married (ref)	–	–	–	–
Education				
Less secondary	1.16	4.60	<0.001	1.09–1.23
Second school	1.08	1.81	0.071	0.99–1.18
Some postsecondary	1.26	3.93	<0.001	1.12–1.42
Postsecondary (ref)	–	–	–	–
Chronic condition				
One or more	1.45	9.22	<0.001	1.34–1.58
Type of drinker				
Regular	0.86	-3.13	0002	0.78–0.94
Occasional	0.91	-1.86	0.063	0.82–1.00
Former	1.10	2.06	0.039	1.00-1.20
Never	–	–	–	–
Smoker				
Yes	1.77	17.72	<0.001	1.66–1.89
No (ref)	–	–	–	–
Physical activity				
Moderate	0.77	-7.38	<0.001	0.72–0.83
Active	0.69	-9.61	<0.001	0.64–0.74
Inactive (ref)	–	–	–	–

[a]Age is treated as a continuous variable in these models.

Note: "ref" refers to the control group used as the reference.

After analyzing age- and sex-adjusted hazard ratio models, we examined a model that included adjustments for all variables (sex, age, marital status, education, chronic condition, type of drinker, and smoking frequency). Elevated mortality in MDD continued to be observed (HR = 1.36, $p < 0.0001$), as shown in **Table 3**. Thus, being physically active was protective (HR = 0.69, $p < 0.0001$), as was being moderately active (HR = 0.77, $p < 0.0001$), with adjustment for the set of covariates available in this study.

3.2. Canadian Community Health Survey—Mental Health (2012)

There was a past-year prevalence of MDD of 4.7%, similar to that observed in the 2002 survey. The prevalence of depression varied across different demographics in a manner consistent with the 2002 data. Notably, those who engaged in moderate PA reported a prevalence of 5.4%, while inactive individuals showed a slightly lower prevalence of 5.2%. Individuals who were highly active physically demonstrated a prevalence of 4.2%, and those who were moderately active exhibited a prevalence of 3.5%. Furthermore, the data indicates that depression was more pronounced among specific subgroups. Females exhibited a higher prevalence at 5.8%, and individuals within the middle age group (40–49 years) reported a prevalence of 6.8%. Those who were divorced also showed a 6.8% prevalence of depression, while individuals with some postsecondary education but no university or college degree recorded a prevalence of 8.5%. Other groups, such as underweight individuals (6.5%), former alcohol users (6.0%), and smokers (7.9%), also demonstrated a higher prevalence of past-year major depression. For additional information, refer to **Table 2**. The frequencies of deaths during follow-up (five years) among those who were depressed were 4.1%, compared to 3.5% among those without major depression.

Initially, we estimated the HR for depression while adjusting for age and sex (HR = 3.11, $p < 0.0001$). Subsequently, when we incorporated PA levels into the model, along with the corresponding interaction term, the analysis revealed that these interaction terms were not statistically significant, indicating a lack of multiplicative interaction ($p > 0.05$). Upon removal of these interaction terms, the HRs for PA emerged as significant. This updated model with PA levels exhibited a slight attenuation in the association between major depression and elevated mortality, resulting in an (HR = 2.96, $p < 0.0001$), as detailed in **Table 4**. Specifically, being highly active physically showed a

protective effect (HR = 0.47, $p < 0.0001$), as did being physically active (HR = 0.53, $p < 0.0001$) and moderately active (HR = 0.49, $p < 0.0001$). Following the examination of hazard ratios adjusted for age and sex, we proceeded to analyze a model adjusted for all available covariates, similar to the CCHS 2002 (see **Table 4**). In this more inclusive analysis, the association between major depression and elevated mortality persisted (HR = 2.19, $p < 0.0001$). Thus, being very active physically (HR = 0.55, $p < 0.0001$), active (HR = 0.57, $p < 0.0001$), and moderately active (HR = 0.59, $p < 0.0001$) continued to be associated with lower mortality.

Table 4 • Association of physical activity with major depression-associated mortality: Cox proportional hazard models based on the linkage of the CCHS-MH 2012 to vital statistics data

CCHS-MH 2012				
	HR	***Z***	***p* Value**	**LCI–UCI**
Model 1				
Major depression	3.11	4.93	<0.001	1.98–4.88
Male sex	1.85	6.82	<0.001	1.55–2.22
Age[a]	1.10	27.03	<0.001	1.09–1.11
Model 2				
Major depression	2.96	4.36	<0.001	1.81–4.82
Male sex	2.01	7.39	<0.001	1.67–2.42
Age[a]	1.10	24.81	<0.001	1.09–1.11
Inactive (ref)	–	–	–	–
Moderate	0.49	−5.72	<0.001	0.38–0.62
Active	0.53	−3.73	<0.001	0.38–0.74
Very active	0.47	−5.71	<0.001	0.37–0.61
Model 3				
Major depression	2.18	2.88	0.004	1.29–3.70
Male sex	2.30	8.01	<0.001	1.87–2.82
Age[a]	1.10	23.56	<0.001	1.09–1.11
Marital status				
Single	1.71	2.83	0.005	1.18–2.50
Divorced	1.28	2.49	0.013	1.05–1.56
Married (ref)	–	–	–	–
Education				
Less secondary	0.99	−0.03	0.976	0.80–1.22
Second school	1.25	1.62	0.104	0.95–1.64
Some postsecondary	1.10	0.31	0.759	0.58–2.10
Postsecondary (ref)	–	–	–	–
Chronic condition				
Have one or more	1.96	4.48	<0.001	1.46–2.63
Type of drinker				
Regular	0.59	−4.65	<0.001	0.47–0.73
Occasional	0.80	−1.86	0.062	0.63–1.01
None or former	–	–	–	–
Smoker				
Current	1.77	5.65	<0.001	1.75–3.20
Former	1.17	1.39	0.165	0.93–1.46
Never (ref)	–	–	–	–
Physical activity				
Moderate	0.59	−4.13	<0.001	0.46–0.76
Active	0.57	−3.86	<0.001	0.43–0.75
Very active	0.55	−4.65	<0.001	0.43–0.70
Inactive (ref)	–	–	–	–

[a]Age is treated as a continuous variable in these models.

Note: "ref" refers to the control group used as the reference.

The analysis of RERI was based on the age- and sex-adjusted models (Model 1 in **Tables 3** and **4**). The analysis yielded negative results. Specifically, for the CCHS 2002, we found RERI = 0.45, $p = 0.125$, and for the CCHS-MH 2012, we found RERI = 0.61, $p = 0.744$.

4. Conclusions

This is the first study to assess the protective effects of PA against elevated mortality in individuals with MDD, as evaluated through a diagnostic interview across all ages (15+). The results from the CCHS 2002 indicate that being physically active or moderately active is associated with lower mortality, independent of MDD, with no interaction observed between PA and MDD on either the multiplicative or additive scales. In the same context, regardless of depression status, results from the CCHS-MH 2012 study show that being very active (45%), active (43%), or moderately active (41%) is associated with lower mortality. Following the current recommendations for PA >150 min should be the minimum target to achieve benefits [20]. However, we also highlight that even without meeting the full PA guidelines, there are still benefits in reducing mortality.

A robust body of evidence has shown that PA may decrease mortality rates. Our study investigated the protective effect of being physically active, including three PA levels: very active, active, and moderately active, on elevated mortality in MDD. Considering data from the CCHS 2002, our results indicate that following current health recommendations or even being below recommendations but not entirely inactive may lower mortality risk by 36% and 29% when controlled for sex and age, respectively. PA continues to have a protective effect on mortality independent of MDD and the mortality determinants measured in this study, a statement that applies both to physically active (31%) and moderately active (23%) participants.

This study adds to the literature by demonstrating substantial benefits in a representative sample drawn from the general population. The 5–10% of the population that experience major depressive episodes can benefit from PA, which is a substantial proportion of the population. Although the RERI results do not provide statistical confirmation of synergy, this does not negate the importance of the protective effect of PA on mortality.

The protective effects reported here should be considered conservative estimates, since some of the effects of MDD on mortality may be mediated by other determinants. For example, MDD increases the incidence of chronic diseases and smoking

persistence, both of which can partially mediate the MDD–mortality association. Additionally, after an 11-year interval, data from the CCHS-MH 2012 continues to underscore the enduring protective impact of PA on mortality, independent of its influence on depression. It is noteworthy that when a more robust statistical model was applied, including potential covariates similar to those used in the CCHS 2002 analysis, the hazard ratios increased substantially (HR = 2.18). Despite this elevation in mortality risk, it is worth highlighting that PA levels exhibited even greater protective effects after a decade. In practical terms, adhering to PA recommendations (e.g., even slightly below or above 150 min/week) may yield a substantial 40–45% reduction in the risk of mortality.

Furthermore, to delve deeper into our findings, we conducted an analysis aimed at evaluating the relative excess risk resulting from the interaction between PA levels and their association with mortality in major depression. While the interaction model did not yield statistically significant results, our exploratory analysis did reveal a possible greater-than-additive interaction, indicating a heightened risk of mortality in both the CCHS 2002 (RERI = 0.45) and CCHS-MH 2012 (RERI = 0.61) datasets. Although our results are consistent with the greater-than-additive interaction reported by Liu et al., the lack of statistical significance means that our results did not replicate this finding decisively.

Physical inactivity causes economic and social losses and increases mortality, regardless of mental health status [43, 44]. Physical activity may protect against mortality through multiple pathways, including the reduction of risk factors for mortality, such as cardiovascular disease, diabetes, and other noncommunicable diseases. In addition to prevention, regular PA may help to manage several health conditions, preventing the progression of comorbidities associated with chronic diseases. For example, there is a high prevalence of hypertension, diabetes, and other chronic diseases among individuals with MDD [45–48]. These chronic conditions may improve when PA levels follow the World Health Organization (WHO) recommendations [20]. Regular PA stimulates mechanisms, including improvements in vascular endothelial function, structural vascular adaptations, cardioprotection, and improved autonomic balance (e.g., increases vagal tone to the heart) [49]. In addition, PA may promote a reduction in inflammation (e.g., cytokines). If uncontrolled, acute inflammation can become chronic, potentially reducing the effectiveness of the anti-inflammatory response [50]. During PA, muscles act on immune receptors by secreting muscle-specific cytokines or “myokines”, which may have local and systemic influences on inflammation and metabolism [51]. From a neurobiological perspective, PA may contribute to increased neuroplasticity involving brain-derived neurotrophic factor and increased blood flow to the brain, which may provide neuronal support to prevent atrophy in brain regions associated with several types of mental disorder, including depression [52, 53]. In this perspective, PA might regulate serotonergic and dopaminergic levels, which are associated with improved mood and stress response [54, 55]. Additionally, we highlight the effect of PA on cognitive function, which enhances an individual’s ability to produce appropriate responses to the environment [56].

Symptoms of depression, such as fatigue, anhedonia, and hopelessness, may interfere with participation in PA. Specialized interventions capable of overcoming these barriers should be developed and implemented in psychiatric treatment settings. Benefits may include improved mental health outcomes and reduced all-cause mortality.

Our study has some limitations. First, the baseline data is limited by the cross-sectional nature of the study, which did not include certain important populations (e.g., residents of institutions). Second, although the study included several questions related to the intensity, frequency, and type of PA, the questionnaire was not validated and did not include objective measures of PA (e.g., accelerometer). Additionally, there were differences in the PA questions between the 2002 and 2012 surveys. Therefore, future epidemiological studies should apply direct measures to provide more accurate quantification of PA levels in a population. Additionally, since inflammation may partially mediate the association between MDD and mortality, future studies may benefit from measuring pro-inflammatory biomarkers. Given that the limitations of PA measurement apply equally to both depressed and nondepressed participants, any bias arising from the misclassification of PA status would likely be non-differential. This could lead to a dilution of the HRs, potentially underestimating the benefits of PA. Furthermore, as the survey datasets are cross-sectional, they cannot fully clarify temporal relationships. In some cases, medical conditions or injuries may have limited participants’ PA, and the treatment of depression could not be clearly delineated using the survey data.

In conclusion, regardless of MDD, following PA recommendations of >150 min/week or even engaging in less than the recommended levels of PA may contribute to a greater protective impact against elevated mortality and reduce health-related risk factors, thereby enhancing overall health and well-being. Strategies to reduce physical inactivity and promote PA should be encouraged. Every step is important, and engaging in some PA is better than none.

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Author contributions

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

Data supporting these findings are available within the article, at https://doi.org/10.20935/MHealthWellB7335, or upon request.

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