Original Article

Eating Timing and Frequency as a Predictor of Hospitalization and/or Mortality From Coronary Artery Disease: The Linked CCHS-DAD-CMDB 2004-2013 Study

Allie S. Carew, MSc,[a,b,c] Rania A. Mekary, PhD,[d] Susan Kirkland, PhD,[a,c] Olga Theou, PhD,[b,c,e] Robin Urquhart, PhD,[a,c,f] Ratika Parkash, MD, MS,[b,c] and Leah E. Cahill, PhD, RD[a,b,c]

[a] Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada

[b] Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

[c] QEII Health Sciences Centre, Nova Scotia Health Authority, Halifax, Nova Scotia, Canada

[d] School of Pharmacy, Massachusetts College of Pharmacy and Health Sciences University, Boston, Massachusetts, USA

[e] School of Physiotherapy, Dalhousie University, Halifax, Nova Scotia, Canada

[f] Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada

ABSTRACT

Background: Coronary artery disease (CAD) is a major overlapping challenge in both clinical and public health realms due to high rates of hospitalization and mortality. Despite nutrition being a key risk factor for CAD, little is known about eating timing and frequency in Canadians or their relation to risk of hospitalization and/or mortality from CAD.

Methods: Breakfast consumption, between-meal consumption, eating frequency, and established CAD risk factors were assessed at baseline in 13,328 adults free of cancer and CAD from the 2004 Canadian Community Health Survey, Cycle 2.2, Nutrition Focus and were linked to administrative health databases to determine incidence of hospitalization and/or mortality from CAD in the following 9 years. Multivariable-adjusted hazard ratios with 95% confidence intervals estimated from Cox proportional hazards models were computed to

RÉSUMÉ

Introduction : La maladie coronarienne (MC) est un enjeu majeur chevauchant les domaines clinique et de santé publique en raison des taux élevés d'hospitalisation et de mortalité. Bien que la nutrition soit un facteur de risque fondamental de la MC, on en connaît peu sur le moment et la fréquence de la consommation d'aliments chez les Canadiens ou sur leur relation au risque d'hospitalisation et/ou de mortalité en raison de la MC.

Méthodes : Nous avons initialement évalué la prise du déjeuner, la consommation entre les repas, la fréquence de la consommation d'aliments et les facteurs de risque établis de MC de 13 328 adultes indemnes de cancer et de MC de l'Enquête sur la santé dans les collectivités canadiennes de 2004, cycle 2.2, volet nutrition, et avons lié les bases de données administratives en santé pour déterminer la fréquence d'hospitalisation et/ou de mortalité en raison de la MC dans

Cardiovascular disease is a leading cause of admission to the hospital, disability, and premature death, for both women and men in North America,[1,2] causing an estimated economic burden of $351.3 billion in the US[3] and $21.2 billion in Canada.[4] Coronary artery disease (CAD) is the foremost cause of cardiovascular mortality[5] and occurs as the result of a

complicated cardiometabolic disease progression that begins with multiple potential overlapping risk factors. Diet has been identified as an important modifiable risk factor for CAD,[6,7] and many previous dietary studies have established which foods and nutrients contribute to CAD morbidity and mortality prevention. However, little is known about the influence of the timing and/or frequency of consuming meals, snacks, and caloric beverages on CAD outcomes. To date, no evidence-based recommendations exist for adults regarding eating timing and/or frequency for CAD prevention, owing to a limited number of studies on the topic.[8] A 2017 scientific statement on meal timing and frequency from the American Heart Association detailed why this is a priority topic for high-impact research, as much is still unknown.[8]

The prevalence of skipping breakfast has steadily increased among North American adults over the past decades,

test for associations between eating timing/frequency and hospitalization and/or mortality from CAD (n = 746 cases).
Results: Skipping breakfast (12.0% of participants) and engaging in between-meal consumption (90.2%) were common practices, as was eating 4-5 times per day (55.2%). Skipping breakfast, between-meal consumption, and eating more or less than 4-5 times/day were strongly and bi-directionally associated with many sociodemographic, lifestyle, and metabolic risk factors at baseline. No associations were observed between skipping breakfast, between-meal consumption, or eating frequency and risk of hospitalization and/or mortality from CAD.
Conclusions: Skipping breakfast, between-meal consumption, and eating frequency were associated with numerous established risk and preventative factors for CAD at baseline but were not directly associated with the risk of hospitalization and/or mortality from CAD in this cohort of Canadian adults.

les neuf années subséquentes. Nous avons calculé les rapports de risque ajustés à plusieurs variables à intervalles de confiance à 95 % estimés à partir des modèles à risques proportionnels de Cox pour vérifier les associations entre le moment et la fréquence de la consommation d'aliments et l'hospitalisation et/ou la mortalité en raison de la MC (n = 746 cas).
Résultats : L'absence du déjeuner (12,0 % des participants), la consommation d'aliments entre les repas (90,2 %) et la consommation d'aliments de 4 à 5 fois par jour (55,2 %) étaient des pratiques courantes. L'absence du déjeuner, la consommation d'aliments entre les repas et la consommation d'aliments plus ou moins 4-5 fois/jour étaient fortement et bidirectionnellement associées aux facteurs de risque sociodémographiques, liés au mode de vie et métaboliques initiaux. Nous n'avons observé aucune association entre l'absence du déjeuner, la consommation d'aliments entre les repas ou la fréquence de la consommation d'aliments, et le risque d'hospitalisation et/ou de mortalité en raison de la MC.
Conclusions : L'absence du déjeuner, la consommation d'aliments entre les repas et la fréquence de la consommation d'aliments étaient associées à de nombreux risques établis et de facteurs préventifs initiaux de la MC, mais n'étaient pas directement associées au risque d'hospitalisation et/ou de mortalité en raison de la MC dans cette cohorte d'adultes canadiens.

alongside a parallel rise in snacking.[9-13] These trends may have consequences at a population level, because accumulating evidence from short-duration trials, cross-sectional studies, and small prospective studies suggests that eating habits such as snacking and skipping meals are adversely associated with several biomarkers and cardiometabolic risk factors, including ghrelin secretion,[14] weight gain,[15-18] dyslipidemia,[19,20] blood pressure,[21] insulin resistance,[19,20] and type 2 diabetes.[22] Conversely, eating plans that involve intermittent fasting regimens (modifying eating timing and frequency patterns by engaging in periods of abstinence from food and caloric beverages) have been associated with improvements in insulin sensitivity,[23] blood pressure,[24] and blood lipid profiles[25] in adults, and animal studies report that periods of fasting can improve metabolic health indicators and counteract disease processes.[26,27] However, evidence on the long-term effects of these eating plans on cardiometabolic health outcomes is limited.[28] Skipping breakfast, which is often defined as the first meal of the day that breaks the fast after the longest period of sleep and occurs within 2 to 3 hours of awakening,[8] is a common component of some intermittent fasting methods.[29] Of note, long-term human intervention studies of eating plans that involve fasting are rare, because of ethical and feasibility reasons. The few prospective cohort studies of eating timing and frequency and risk of incident CAD events (such as a myocardial infarction) reported inconclusive results,[30-32] although the topic has not yet been researched among solely the most extreme cases causing hospitalization and mortality, or in a Canadian population. Definitions of eating timing and frequency patterns (breakfast, eating occasions, snacks, and meals) and CAD varied across these studies, making comparison among them difficult.[8] To add to the controversy over whether these eating and frequency patterns can have beneficial or detrimental health effects, several potential confounding factors, such as sociodemographic and lifestyle factors, cannot yet be ruled out as influencers of the relationship between eating timing and frequency patterns and cardiometabolic health. The objectives of our study were as follows: (i) to characterize the eating timing and frequency patterns, including skipping breakfast, between-meal consumption, and eating frequency, in a Canadian cohort of diverse socioeconomic status with publicly funded healthcare; and (ii) to prospectively determine whether skipping breakfast, eating infrequently, and between-meal consumption were associated with long-term increased or decreased risk of hospitalization and/or mortality from CAD in this cohort.

Methods

Data sources and study population

The dataset analyzed in the present study was the linked Canadian Community Health Survey-Discharge Abstract Database-Canadian Mortality Database 2004-2013 (CCHS-DAD-CMDB), which is a population-based dataset probabilistically linked using birthdate, sex, and postal code information by Statistics Canada for the fiscal years 2003/2004 to 2012/2013 (the last year of follow-up data currently available in the dataset).[4] This dataset consists of a population-based Canadian cohort, with information on baseline characteristics (participant sociodemographic factors, lifestyle factors, and dietary assessments) from the 2004 Canadian Community Health Survey, Cycle 2.2, Nutrition Focus (CCHS 2.2) and subsequent information on hospitalizations and death records for the 9 years following. As previously described,[5-7] Statistics Canada allows researchers access to this CCHS-DAD-CMDB dataset at their Research Data Centres, which are secure computing facilities that house Statistics Canada's confidential microdata; researchers can apply for access to de-identified data files for analysis. Participants included in the linked dataset provided consent to share and link their data to administrative health data.

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Detailed descriptions of the sampling strategy, recruitment process, design, and methods of the CCHS 2.2 have been published previously.[2] Briefly, the CCHS 2.2 targeted people of all ages who were living in private dwellings in the 10 Canadian provinces. The survey is representative of 98% of the Canadian population living in the provinces but did not include full-time members of the Canadian Armed Forces or people living in the territories, on First Nations Reserves or Crown Lands, in institutions, or in some remote areas. The sample was designed to be representative of the Canadian population in terms of age, sex, geography, and socioeconomic status.[3] The survey consisted of 2 components: a 24-hour dietary recall (a subsample of $\sim 31\%$ of participants completed a second 24-hour dietary recall 3 to 10 days later) and a general health questionnaire that collected information on sociodemographic characteristics, chronic conditions, anthropometric measures, physical activity, alcohol consumption, and smoking, among other variables. Trained Statistics Canada personnel conducted the computer-assisted interviews in-person on all days of the week (including weekend days) in the participants' homes. The Discharge Abstract Database (DAD) is maintained by the Canadian Institute of Health Information (CIHI) and contains information on diagnoses, treatment, length of stay, and discharge status for all individuals admitted to the hospital in all provinces except Quebec. The Canadian Mortality Database (CMDB) is a census of all registered deaths in Canada that includes the underlying and supporting cause and date of death and demographic information, such as name, date of birth, and postal code at the time of death. Deaths occurring in Canada are reported by the provincial and territorial Vital Statistics Registries to Statistics Canada and are then entered into the CMDB.

Participants were excluded from the present analysis if they were < 18 years old, were residents of Quebec (due to a lack of corresponding hospitalization data in the DAD), had self-reported prevalent heart disease at baseline, had self-reported cancer at baseline, reported implausible energy intakes of < 500 or > 5000 kcal per day, as is a common practice in nutrition studies,[33-36] or did not provide consent to share their survey information with provincial and federal ministries of health and to link their responses to administrative health data. After exclusions, the final sample size was 13,328 CCHS 2.2 participants. Statistics Canada granted ethical approval and access to the de-identified linked dataset for the present project (under project number 18-SSH-DAL-5581), and all analyses were conducted at the Atlantic Research Data Centre.

Eating patterns and other dietary assessment

Dietary intake data were collected using a modified version of the US Department of Agriculture Automated Multiple-Pass Method (AMPM) for 24-hour dietary recall, which is an automated 5-step computerized recall method that uses multiple memory cues to maximize a participant's ability to recall all foods eaten in the previous 24 hours. For each food and beverage item reported, participants were asked to self-define the eating occasion and time of food consumption by answering the following 2 questions: (i) "What would you call this eating occasion? Breakfast, lunch (dinner), supper (dinner), brunch, between-meal consumption, drink, extended consumption, other"; and (ii) "About what time did you begin to eat/drink food item(s)?" The time of food consumption was indicated according to the 24-hour clock. In this study, we defined breakfast consumption as a positive response to breakfast or brunch. Breakfast, lunch, supper, and brunch were considered meals, whereas snacks, drinks (containing calories), extended consumption (eating or drinking was continuous throughout the day), and other were combined and considered between-meal consumption.[37,38] Consumption of a food or beverage item (except plain drinking water) was considered a separate eating occasion if it was separated in time from the preceding and succeeding reported eating occasion by at least 60 minutes, a time interval that has been used previously to distinguish eating occasions.[39] We totaled the number of meals and between-meal consumption occasions reported by each participant to calculate eating frequency.

Nutrient and energy intakes for each participant (covariables in the present study) were calculated by Statistics Canada using the Canadian Nutrient File, version 2001b,[40] which is a computerized, bilingual food composition database containing average values for nutrients in foods commonly consumed in Canada.

Measurement of covariables

Information on sociodemographic characteristics (age, sex, racial group, immigrant status, marital status, education, food security, household income before taxes), lifestyle and mental health factors (physical activity index, smoking status, alcohol intake, life stress), and health conditions (high blood pressure, diabetes) was collected by using the general health questionnaire component of the CCHS 2.2. Total daily energy-expenditure values (kcal/kg per day) were used to calculate a physical activity index ("active" = $\geq$ 3.0 kcal/kg per day, "moderate" = 1.5-2.9 kcal/kg per day, "inactive" = < 1.5 kcal/kg per day). Body mass index (BMI) was calculated by dividing participants' weight in kilograms by their height in metres squared (kg/m^2; < 18.5, 18.5-24.9, 25-29.9, $\geq$ 30). Diagnoses of high blood pressure and diabetes were self-reported by the participant.

CAD hospitalization and/or death ascertainment

Hospitalization and cause-of-death information was coded using the Canadian version of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10-CA) in the 9-year follow-up period. Specifically, participants with ICD-10-CA codes of I21, I22, I24, and I25 from the DAD and CMDB, and Canadian Classification of Health Interventions codes 1.IJ.76, 1.IJ.50, 1.IJ.55, and 1.IJ.57 from the DAD, were identified as a case of hospitalization and/or mortality from CAD. We also conducted a sensitivity analysis in which we added hospitalization and/or mortality from angina (ICD-10-CA code I20) to the outcome definition. Data were not available on cases of CAD that did not require hospitalization or result in death. All diagnoses (not only primary diagnoses) were included. Participants were observed for up to 9 years and contributed follow-up time from the date they participated in the CCHS 2.2 until the date of first documented hospitalization and/or death from CAD, date of death from non-CAD causes, or end of the follow-up period (March 31, 2013), whichever came first.

Statistical analysis

We used Stata 16.1 software (StataCorp, College Station, TX) to conduct all statistical analyses, according to an analysis plan developed *a priori*. All analyses were conducted at a 2-tailed alpha level of 0.05. We chose to analyze the data using a cohort-based approach, and therefore all analyses were unweighted. To investigate the validity of a single administration of a 24-hour dietary recall to measure eating timing and frequency, we used Cohen's kappa statistic to assess the agreement of the first 24-hour dietary recall with the CCHS 2004's second 24-hour recall, which was conducted on a subsample of individuals (~30% of participants). We grouped participants based on breakfast-eating status (yes, no) and summarized baseline characteristics, comparing the 2 groups using Student *t* tests or Wilcoxon rank-sum tests for continuous variables, and χ^2 tests for categorical variables. We also summarized baseline characteristics according to eating frequency (total eating occasions per day; $\leq$ 3, 4-5, $\geq$ 6), comparing the 3 groups using 1-way analysis of variance or Kruskal-Wallis tests for continuous variables, and χ^2 tests for categorical variables.

To quantify the risk of incident hospitalization and/or mortality from CAD associated with eating patterns, we used stepwise multivariable-adjusted Cox proportional hazard regression models to estimate adjusted hazard ratios and 95% confidence intervals (CIs). The proportional hazards assumption was verified using Schoenfeld residuals. In the basic multivariate model 1, we adjusted for age (years) and sex. In multivariate model 2, we adjusted for the following demographic factors: predominant racial group (white [yes, no]); immigrant (yes, no, missing); marital status (married/common-law, not married/common-law [widowed, separated, divorced, single, never married], missing); education ($\leq$ secondary school graduation, > secondary school graduation, missing); food security (secure, insecure, missing); household income before taxes (< $15,000, $15,000-$29,999, $30,000-$49,999, $50,000-$79,999, $\geq$ $80,000, missing). In multivariate model 3, we further adjusted for the following baseline lifestyle and mental health factors: smoking (never, past, current, missing); alcohol intake (0-3 times per month, 1-3 times per week, 4+ times per week, missing); physical activity index (active, moderately active, inactive, missing); and life stress (not at all stressful, not very stressful, a bit stressful, quite a bit or extremely stressful, missing). In multivariate model 4 (our main model reported for this study), we further adjusted for the following baseline dietary factors: consumption of sugar-sweetened beverages (yes, no); fruit and vegetable intake (total number of times per day); energy intake (kcal per day); and eating frequency (times per day). High blood pressure (yes, no, missing), diabetes (yes, no, missing), and BMI (kg/m², < 18.5, 18.5-24.9, 25-29.9, $\geq$ 30, missing) are potential mediators and were adjusted for in subsequent Cox regression models to test whether our results were materially altered by their inclusion. This method of examining potential mediation was used in previous studies of eating timing and frequency.[30,32,41,42] In models in which eating frequency was the main exposure, we also adjusted for breakfast (yes, no). Values were coded as "missing" if they were unavailable at baseline (< 1% for most covariates; < 10%-14% for household income and BMI).

Results

In this cohort of 13,328 adults (> 20% of whom were aged $\geq$ 65 years at baseline), 1597 (12.0%) reported skipping breakfast on the day of the 24-hour dietary recall (Table 1), and 1301 (9.8%) reported no between-meal consumption. Of participants, 2497 (18.7%) reported eating $\leq$ 3 times, 7357 (55.2%) reported eating 4-5 times, and 3474 (26.1%) reported eating $\geq$ 6 times (Table 2). We found fair agreement between the two 24-hour dietary recalls with respect to breakfast consumption (percent agreement: 86.5%, Cohen's kappa: 0.33, standard error: 0.02), between-meal consumption (percent agreement: 83.7%, Cohen's kappa: 0.22, standard error: 0.02, and eating frequency (percent agreement: 53.4%, Cohen's kappa: 0.22, standard error: 0.01). Breakfast-nonconsumer and breakfast-consumer groups significantly differed in all the 27 baseline variables compared. Of note, breakfast skippers had higher frequencies of some well-established CAD risk factors, such as smoking, not being in the major racial group (white), food insecurity, less dietary fibre intake, more sugar-sweetened food intake, and less education than participants who reported that they ate breakfast. Breakfast skippers also were younger (median of 33 years vs 49 years), were less likely to be an immigrant, consumed fewer calories, and had a lower frequency of hypertension or diabetes. Between-meal consumption and eating frequency were similarly associated with many baseline variables that are known to both increase and decrease risk of CAD. For example, participants who reported between-meal consumption also reported higher levels of stress, alcohol intake, and physical activity compared to those who did not report between-meal consumption. Eating frequency was inversely associated with food insecurity, alcohol intake, and male sex, and directly associated with fibre intake, physical activity, and being in a married/common-law relationship.

During 9 years of follow-up, 746 CAD-related hospitalizations and/or deaths were documented. No association was observed between skipping breakfast and risk of hospitalization and/or mortality from CAD (hazard ratio [HR] = 1.00, 95% confidence interval [CI]: 0.71-1.40) in any of the models (Table 3). Likewise, no association was observed between between-meal consumption and risk of hospitalization and/or mortality from CAD (HR 1.03, 95% CI: 0.79-1.34; Table 3). We also did not observe an association between eating frequency and risk of CAD hospitalization and/or mortality (Table 4); compared with participants who ate $\leq$ 3 times per day, participants who ate 4-5 times per day had a multivariable HR of 0.94 (95% CI: 0.71-1.25), and participants who ate $\geq$ 6 times per day had an HR of 0.84 (95% CI: 0.50-1.41). Including hospitalization and/or mortality from angina in our outcome definition resulted in an additional 30 cases (n = 776) but did not materially alter our results (Supplemental Tables S1 and S2).

Discussion

To the best of our knowledge, our study is the first to characterize eating timing and frequency in a Canadian cohort and assess whether skipping breakfast, between-meal consumption, and eating frequency are prospectively related to an increased risk of hospitalization and/or mortality from CAD. In this large prospective study of a Canadian cohort with 9

Table 1. Characteristics of the 2004 Canadian Community Health Survey (CCHS): nutrition participants at baseline, by breakfast consumption status and between-meal consumption status

Characteristics	Breakfast consumption			Between-meal consumption		
	No (n = 1597)	Yes (n = 11,731)	P	No (n = 1301)	Yes (n = 12,027)	P
Age, y	33 (22, 48)	49 (31, 66)	< 0.001	52 (31, 70)	47 (29, 63)	< 0.001
Sex			< 0.001			0.321
Male	836 (52.4)	4974 (42.4)		584 (44.9)	5226 (43.5)	
Female	761 (47.7)	6757 (57.6)		717 (55.1)	6801 (56.6)	
Immigrant to Canada	186 (11.7)	1871 (16.0)	< 0.001	226 (17.4)	1831 (15.2)	0.024
Largest racial group (white)			< 0.001			0.205
No	269 (16.8)	1345 (11.5)		175 (13.5)	1439 (12.0)	
Yes	1327 (83.1)	10,380 (88.5)		1126 (86.6)	10,581 (88.0)	
Urban residence	1247 (78.1)	8885 (75.7)	0.040	1005 (77.3)	9127 (75.9)	0.275
Food insecure	197 (12.3)	778 (6.6)	< 0.001	99 (7.6)	876 (7.3)	0.884
Current smoker	730 (45.7)	2704 (23.1)	< 0.001	297 (22.8)	3137 (26.1)	0.037
Alcohol use, times per wk			< 0.001			< 0.001
None	249 (15.6)	2538 (21.6)		371 (28.5)	2416 (20.1)	
< 1	703 (44.0)	4775 (40.7)		495 (38.1)	4983 (41.4)	
1−3	505 (31.6)	3101 (26.4)		325 (25.0)	3281 (27.3)	
4+	139 (8.7)	1306 (11.1)		108 (8.3)	1337 (11.1)	
Self-perceived stress			< 0.001			< 0.001
Not at all stressful	174 (10.9)	1473 (12.6)		215 (16.5)	1432 (11.9)	
Not very stressful	332 (20.8)	3102 (26.4)		356 (27.4)	3078 (25.6)	
A bit stressful	683 (42.8)	4779 (40.7)		498 (38.3)	4964 (41.3)	
Quite a bit stressful*	329 (20.6)	2024 (17.3)		232 (17.8)*	2543 (21.1)*	
Extremely stressful*	78 (4.9)	344 (2.9)				
Physical activity index			< 0.001			0.048
Active	273 (17.1)	2331 (19.9)		233 (17.9)	2371 (19.7)	
Moderate	376 (23.5)	2940 (25.1)		303 (23.3)	3013 (25.1)	
Inactive	946 (59.2)	6459 (55.1)		764 (58.7)	6641 (55.2)	
Married/common-law	606 (38.0)	5940 (50.6)	< 0.001	572 (44.0)	5974 (49.7)	< 0.001
Household income, $			0.014			< 0.001
< 15,000	181 (11.3)	1179 (10.1)		167 (12.8)	1193 (9.9)	
15,000−29,999	273 (17.1)	2225 (19.0)		270 (20.8)	2228 (18.5)	
30,000−49,999	354 (22.2)	2494 (21.3)		285 (21.9)	2563 (21.3)	
50,000−79,999	333 (20.9)	2647 (22.6)		259 (19.9)	2721 (22.6)	
≥ 80,000	276 (17.3)	2110 (18.0)		174 (13.4)	2212 (18.4)	
Missing	180 (11.3)	1076 (9.2)		146 (11.2)	1110 (9.2)	
Education			< 0.001			< 0.001
< Secondary school graduation	403 (25.2)	2840 (24.2)		421 (32.4)	2822 (23.5)	
Secondary school graduation	388 (24.3)	2232 (19.0)		252 (19.4)	2368 (19.7)	
Some postsecondary	247 (15.5)	1157 (9.9)		109 (8.4)	1295 (10.8)	
Postsecondary graduation	543 (34.0)	5411 (46.1)		507 (39.0)	5447 (45.3)	
BMI, kg/m^2	25.7 (22.8, 29.7)	26.2 (23.1, 29.9)	0.033	26.4 (23.1, 30.1)	26.1 (23.1, 29.8)	0.149
BMI, kg/m^2			0.094			0.313
< 18.5	41 (2.6)	205 (1.8)		30 (2.3)	216 (1.8)	
18.5−24.9	567 (35.5)	4015 (34.2)		419 (32.2)	4163 (34.6)	
25−29.9	480 (30.1)	3718 (31.7)		412 (31.7)	3786 (31.5)	
≥ 30	333 (20.9)	2560 (21.8)		298 (22.9)	2595 (21.6)	
Missing	176 (11.0)	1233 (10.5)		142 (10.9)	1267 (10.5)	
High blood pressure	155 (9.7)	2290 (19.5)	< 0.001	270 (20.8)	2175 (18.1)	0.058
Diabetes	54 (3.4)	765 (6.5)	< 0.001	89 (6.8)	730 (6.1)	0.396
Energy intake, kcal/d	1729.0 (1233.2, 2447.3)	1846.4 (1369.9, 2462.4)	< 0.001	1436.3 (1032.4, 1949.6)	1883.6 (1395.0, 2512.3)	< 0.001

Continued

Table 1. Continued.

Characteristics	Breakfast consumption			Between-meal consumption		
	No (n = 1597)	Yes (n = 11,731)	P	No (n = 1301)	Yes (n = 12,027)	P
Eating frequency, times/d	4 (3, 5)	5 (4, 6)	< 0.001	3 (3, 3)	5 (4, 6)	< 0.001
Between-meal consumption	1495 (93.6)	10532 (89.8)	< 0.001	N/A	N/A	
Fruits and vegetables, times/d	2.7 (1.7, 3.9)	3.9 (2.7, 5.3)	< 0.001	3.5 (2.4, 4.9)	3.7 (2.6, 5.1)	< 0.001
Consumed a sugar-sweetened beverage	795 (49.8)	4028 (34.3)	< 0.001	307 (23.6)	4516 (37.6)	< 0.001
Sodium, mg/d	2543.1 (1629.6, 3716.2)	2693.2 (1862.6, 3783.5)	< 0.001	2262.5 (1504.8, 3238.1)	2722.2 (1877.7, 3823.5)	< 0.001
Sugar, g/d	79.0 (44.1, 129.5)	88.2 (55.7, 133.4)	< 0.001	57.9 (35.1, 90.7)	91.1 (57.4, 136.8)	< 0.001
Fibre intake, g/d	10.9 (6.9, 16.1)	15.0 (10.3, 21.4)	< 0.001	11.6 (7.7, 17.0)	14.9 (10.1, 21.3)	< 0.001
Protein intake, g/d	66.2 (42.9, 94.4)	73.9 (52.3, 102.7)	< 0.001	62.4 (43.1, 92.0)	74.0 (52.3, 102.7)	< 0.001
Carbohydrate intake, g/d	211.3 (141.9, 294.7)	228.0 (167.6, 305.5)	< 0.001	174.3 (122.0, 234.3)	231.7 (170.0, 311.0)	< 0.001
Saturated fat intake, g/d	18.8 (11.2, 29.8)	20.0 (12.7, 30.2)	0.001	15.5 (9.3, 24.2)	20.3 (12.9, 30.8)	< 0.001
Total fat intake, g/d	59.7 (37.7, 92.5)	64.3 (42.5, 93.4)	< 0.001	49.2 (31.8, 74.6)	65.5 (43.4, 95.2)	< 0.001

Values are displayed as mean (standard deviation) or median (interquartile range) for continuous variables and, or n (%) for categorical variables unless otherwise indicated.

BMI, body mass index; N/A, not applicable.

*Quite a bit stressful and extremely stressful were combined due to low cell count.

years of follow-up, we found that most participants consumed breakfast, ate between meals, and ate 4-5 times per day. Interestingly, skipping breakfast, between-meal consumption, and eating less or more than 4-5 times per day were bi-directionally associated with many established risk factors at baseline. We did not detect associations between skipping breakfast, between-meal consumption, and eating frequency and hospitalization and/or mortality from CAD before or after adjustment for sociodemographic factors, lifestyle and mental health factors, and metabolic factors.

Our findings are in alignment with previous studies that have reported on the prevalence of eating timing and frequency behaviours in North Americans[13,43] and that these patterns differ by many sociodemographic and lifestyle factors[12,44-46] that are known to both increase and decrease the risk of CAD.[47,48] Our findings are also in line with those of previous studies on the relationships between skipping breakfast and incidence of cardiovascular disease, but not specifically CAD, eating frequency and CAD,[30] and between-meal consumption and CAD.[30] In a meta-analysis of prospective cohort studies on breakfast consumption and cardiovascular disease morbidity and mortality (including CAD; 4 studies, based on n = 199,634 participants), people who regularly skipped breakfast were at 21% greater risk of incident cardiovascular disease morbidity or mortality than people who regularly consumed breakfast (pooled HR = 1.21, 95% CI: 1.08-1.35; $I^2 = 17.3\%$, $P = 0.304$) after adjustment for various demographic, lifestyle, dietary, and health-related factors.[49] However, unlike in the present study, stroke was included in the definition of cardiovascular disease in 3 of the 4 included studies, which has a modestly different etiologic pathway than CAD. Three of the 4 studies included in the same meta-analysis examined the association between skipping breakfast and CAD separately and found that skipping breakfast was not significantly associated with risk of CAD after adjustment for various potential confounders and/or mediators,[30-32] which is in line with our findings. For example, a recent prospective cohort study of a nationally representative sample of adults in the US indicated that people who never consumed breakfast, compared with those consuming breakfast every day, had a 3.39-fold higher risk of stroke-specific mortality (95% CI: 1.40-8.24), whereas no association was observed between skipping breakfast and heart disease-specific mortality after adjustment for a variety of sociodemographic, lifestyle, dietary, and health factors.[32] In contrast, a large prospective study of > 95% white male health professionals in the US reported that breakfast skippers had a 27% higher risk of CAD compared with breakfast consumers[30]; however, the sample was too homogeneous to assess potential confounding of the relationship between skipping breakfast and CAD by socioeconomic and demographic variables.

Of note, the duration of follow-up in these previous studies was longer than that in the present study. The mean duration of follow-up of the studies included in the meta-analysis was 17.4 years[49] vs a maximum of 9 years in the present study. The prevalence and incidence of CAD increases as people age[3,50]; therefore, our study could have been underpowered for cases of CAD hospitalizations and/or mortality within this shorter follow-up period. We did not have information on cases of CAD that did not require hospitalization or result in

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Table 2. Characteristics of the 2004 Canadian Community Health Survey (CCHS): nutrition participants at baseline, by eating frequency

Characteristics*	Eating frequency, times per day			P
	≤ 3 (n = 2497)	4–5 (n = 7357)	≥ 6 (n = 3474)	
Age, y	46 (27, 64)	48 (29, 65)	48 (32, 61)	< 0.001
Sex				< 0.001
Male	1186 (47.5)	3207 (43.6)	1417 (40.8)	
Female	1311 (52.5)	4150 (56.4)	2057 (59.2)	
Immigrant to Canada	385 (15.4)	1083 (14.7)	589 (17.0)	0.019
Largest racial group (white)				< 0.001
No	368 (14.7)	846 (11.5)	400 (11.5)	
Yes	2129 (85.3)	6506 (88.4)	3072 (88.4)	
Urban residence	1945 (77.9)	5562 (75.6)	2625 (75.6)	0.052
Food insecure	240 (9.6)	519 (7.1)	216 (6.2)	< 0.001
Current smoker	725 (29.0)	1798 (24.4)	911 (26.2)	< 0.001
Alcohol use, times per wk				< 0.001
None	597 (23.9)	1553 (21.1)	637 (18.3)	
< 1	1029 (41.2)	3030 (41.2)	1419 (40.9)	
1–3	664 (26.6)	1965 (26.7)	977 (28.1)	
4+	204 (8.2)	800 (10.9)	441 (12.7)	
Self-perceived stress				< 0.001
Not at all stressful	370 (14.8)	923 (12.6)	354 (10.2)	
Not very stressful	644 (25.8)	1935 (26.3)	855 (24.6)	
A bit stressful	950 (38.1)	3008 (40.9)	1504 (43.3)	
Quite a bit stressful	445 (17.8)	1258 (17.1)	650 (18.7)	
Extremely stressful	87 (3.5)	225 (3.1)	110 (3.2)	
Physical activity index				< 0.001
Active	458 (18.3)	1396 (19.0)	750 (21.6)	
Moderate	566 (22.7)	1835 (24.9)	915 (26.3)	
Inactive	1470 (58.9)	4126 (56.1)	1809 (52.1)	
Married/common-law	1043 (41.8)	3623 (49.3)	1880 (54.1)	< 0.001
Household income, $				< 0.001
< 15,000	330 (13.2)	740 (10.1)	290 (8.4)	
15,000–29,999	474 (19.0)	1404 (19.1)	620 (17.9)	
30,000–49,999	516 (20.7)	1565 (21.3)	767 (22.1)	
50,000–79,999	524 (21.0)	1631 (22.2)	825 (23.8)	
≥ 80,000	366 (14.7)	1307 (17.8)	713 (20.5)	
Missing	287 (11.5)	710 (9.7)	259 (7.5)	
Education				< 0.001
< Secondary school graduation	751 (30.1)	1795 (24.4)	697 (20.1)	
Secondary school graduation	530 (21.2)	1461 (19.9)	629 (18.1)	
Some postsecondary	264 (10.6)	754 (10.3)	386 (11.1)	
Postsecondary graduation	927 (37.1)	3289 (44.7)	1738 (50.0)	
BMI, kg/m²	26.3 (23.2, 30.2)	26.3 (23.1, 29.9)	25.9 (23.0, 29.6)	0.028
BMI, kg/m²				0.287
< 18.5	53 (2.1)	124 (1.7)	69 (2.0)	
18.5–24.9	824 (33.0)	2526 (34.3)	1232 (35.5)	
25–29.9	774 (31.0)	2346 (31.9)	1078 (31.0)	
≥ 30	580 (23.2)	1588 (21.6)	725 (20.9)	
Missing	266 (10.7)	773 (10.5)	370 (10.7)	
High blood pressure	439 (17.6)	1424 (19.4)	582 (16.8)	0.002
Diabetes	138 (5.5)	467 (6.4)	214 (6.2)	0.328
Energy intake, kcal/d	1465.0 (1051.3, 2032.6)	1818.0 (1357.3, 2418.0)	2138.9 (1638.6, 2791.7)	< 0.001
Fruits and vegetables, times/d	3.3 (2.2, 4.6)	3.7 (2.5, 5.0)	4.1 (2.9, 5.6)	< 0.001
Consumed a sugar-sweetened beverage	771 (30.9)	2708 (36.8)	1344 (38.7)	< 0.001
Sodium, mg/d	2216.7 (1442.2, 3187.5)	2678.5 (1864.5, 3764.5)	2993.6 (2115.4, 4168.2)	< 0.001
Sugar, g/d	61.4 (35.6, 97.0)	85.7 (55.0, 128.5)	111.3 (75.0, 158.9)	< 0.001
Fibre intake, g/d	10.9 (7.1, 16.0)	14.4 (9.9, 20.3)	17.7 (12.6, 24.7)	< 0.001
Protein intake, g/d	59.8 (41.0, 89.9)	72.8 (51.6, 100.7)	82.5 (60.3, 111.2)	< 0.001
Carbohydrate intake, g/d	176.1 (122.5, 242.1)	223.3 (165.4, 297.8)	269.9 (204.3, 355.1)	< 0.001
Saturated fat intake, g/d	15.6 (9.7, 24.7)	19.9 (12.7, 29.9)	23.1 (15.0, 34.3)	< 0.001
Total fat intake, g/d	50.3 (32.4, 76.4)	64.1 (42.2, 92.0)	73.8 (50.5, 105.7)	< 0.001

BMI, body mass index.

*Values are displayed as mean (standard deviation) or median (interquartile range) for continuous variables and, or n (%) for categorical variables unless otherwise indicated.

death, meaning we captured the more severe cases of CAD only. This possibility potentially explains our observation of no significant association between skipping breakfast and hospitalization and/or mortality from CAD.

Another potential explanation for the lack of association between eating timing and frequency patterns and risk of

hospitalization and/or mortality from CAD in this study is that eating timing and frequency may be too strongly aligned with other diet-related (eg, food insecurity or diet quality) or CAD-related factors (eg, BMI, hypertension) to assess it independently in this cohort. Eating timing and frequency were associated with both established risk factors and

Table 3. Breakfast and between-meal consumption and multivariable-adjusted hazard ratios (HRs) of hospitalization and/or mortality from coronary artery disease with 95% confidence intervals (CIs)

	Breakfast		P
	No	Yes	
Cases, n	40	706	
Person-years	13,514.5	96,564.0	
Adjusted for age and sex: HR (95% CI)	1.15 (0.83−1.60)	1.00 (Ref)	0.399
+ Demographic factors*	1.13 (0.81−1.57)	1.00 (Ref)	0.473
+ Lifestyle and mental health factors[†]	1.01 (0.72−1.40)	1.00 (Ref)	0.965
+ Dietary factors[‡]	**1.00 (0.71−1.40)**	**1.00 (Ref)**	**0.993**
Additional adjustment for potential mediators			
+ Health conditions[§]	1.01 (0.72−1.41)	1.00 (Ref)	0.971
+ BMI[‖]	1.01 (0.72−1.41)	1.00 (Ref)	0.969

	Between-meal consumption		P
	No	Yes	
Cases, n	87	659	
Person-years	10,518.6	99,560.0	
Adjusted for age and sex: HR (95% CI)	1.00 (Ref)	1.08 (0.87−1.35)	0.489
+ Demographic factors*	1.00 (Ref)	1.08 (0.87−1.36)	0.477
+ Lifestyle and mental health factors[†]	1.00 (Ref)	1.05 (0.84−1.32)	0.664
+ Dietary factors[‡]	**1.00 (Ref)**	**1.03 (0.79−1.34)**	**0.834**
Additional adjustment for potential mediators			
+ Health conditions[§]	1.00 (Ref)	1.03 (0.79−1.34)	0.831
+ BMI[‖]	1.00 (Ref)	1.03 (0.79−1.33)	0.853

Boldface indicates the main model being reported.

BMI, body mass index; Ref, referent.

*In addition to age (years) and sex (male, female), this model is adjusted for the following baseline demographic factors: largest racial group (yes, no); marital status (married, not married); education (≤ secondary school graduation, > secondary school graduation, missing); immigrant (yes, no, missing); food secure (yes, no, missing); and household income (< $15,000, $15,000−$29,999, $30,000−$49,999, $50,000−$79,999, ≥ $80,000, missing).

[†] In addition to age, sex, and baseline demographic factors, this model is further adjusted for the following baseline lifestyle and mental health factors: smoking (never, past, current, missing); alcohol intake (none- < 3 times per month, 1-3 times per week, 4+ times per week, missing); physical activity index (active, moderately active, inactive, missing); and life stress (not at all stressful, not very stressful, a bit stressful, quite a bit or extremely stressful, missing).

[‡] In addition to age, sex, baseline demographic, lifestyle, and mental health factors, this model is further adjusted for the following baseline dietary factors: consumption of sugar-sweetened beverages (yes, no); fruit and vegetable intake (times per day); eating frequency (times per day); sodium (mg per day), sugar (g per day); and energy intake (kcal per day). This is the main model reported for this analysis.

[§] In addition to age, sex, and baseline demographic, lifestyle, mental health, and dietary factors, this model is further adjusted for the following baseline health conditions: high blood pressure (yes, no, missing); and diabetes (yes, no, missing).

[‖] In addition to age, sex, baseline demographic, lifestyle, mental health, and dietary factors, and baseline health conditions, this model is further adjusted for baseline BMI (kg/m^2, < 18.5, 18.5-24.9, 25-29.9, ≥ 30).

preventative factors for CAD at baseline in our study, and these factors could be neutralizing the association between eating timing/frequency and risk of hospitalization and/or mortality from CAD. For example, the mean age of participants reporting that they did not eat breakfast (33 years) was substantially lower than the mean age of participants reporting that they ate breakfast (49 years). Potentially, people with metabolic risk factors, such as older age, high BMI, hyperglycemia, hypertension, or hypercholesterolemia, are more likely to adopt practices generally regarded as "healthy," such as eating breakfast and eating regularly, which could generate a reverse causation type effect such as indication bias.

Limitations and strengths

Our study had several limitations that should be noted. First, misclassification bias may have been present because breakfast consumption, between-meal consumption, and eating frequency were assessed at one point in time via a single administration of a 24-hour dietary recall, which does not capture daily variation or measure habitual dietary intake or patterns. However, we compared the responses of participants who completed both the initial and second 24-hour dietary recalls (n = 3986) and found fair agreement between the 2 recalls with respect to breakfast consumption, between-meal consumption, and eating frequency. Eating timing and frequency patterns may have changed within the 9-year follow-up period; therefore, nondifferential misclassification error may have been present, which would have attenuated true associations. Differential misclassification bias could have also been present if participants who were at high risk of CAD changed their eating habits in response to advice from a healthcare provider during the follow-up period. Second, we cannot rule out possible residual confounding by unknown or unmeasured factors (eg, bodyweight change, familial hypercholesterolemia, sedentary behaviour, shift work, circadian rhythms, light/dark exposure, and sleep pattern). Third, covariates were measured at baseline only; therefore, we were unable to adjust for time-varying confounders. Fourth, the CCHS 2.2 data were not linked to physician billing databases, which provide records of insured services provided by physicians in each province, or insured patient registries, which record longitudinal information regarding the entire population of insured beneficiaries of provincial healthcare services,

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Table 4. Eating frequency and multivariable-adjusted hazard ratios (HRs) of hospitalization and/or mortality from coronary artery disease with 95% confidence intervals (CIs)

| | Eating frequency, times per day | | | | |
	≤ 3	4–5	P	≥ 6	P
Cases, n	136	435		175	
Person-years	20,482.6	60,620.3		28,975.7	
Adjusted for age and sex: HR (95% CI)	1.00 (Ref)	1.02 (0.84–1.24)	0.815	1.01 (0.81–1.26)	0.928
+ Demographic factors*	1.00 (Ref)	1.02 (0.84–1.24)	0.818	1.04 (0.83–1.31)	0.716
+ Lifestyle and mental health factors[†]	1.00 (Ref)	1.03 (0.85–1.25)	0.763	1.02 (0.81–1.28)	0.886
+ Dietary factors[‡]	**1.00 (Ref)**	**0.94 (0.71–1.25)**	**0.688**	**0.84 (0.50–1.41)**	**0.502**
Additional adjustment for potential mediators					
+ Health conditions[§]	1.00 (Ref)	0.92 (0.69–1.22)	0.546	0.79 (0.47–1.33)	0.377
+ BMI[‖]	1.00 (Ref)	0.91 (0.69–1.22)	0.534	0.78 (0.46–1.32)	0.361

Boldface indicates the main model being reported.

BMI, body mass index; Ref, referent.

* In addition to age (years) and sex (male, female), this model is adjusted for the following baseline demographic factors: largest racial group (yes, no); marital status (married, not married); education ($\leq$ secondary school graduation, > secondary school graduation, missing); immigrant (yes, no, missing); food secure (yes, no, missing); and household income (< \$15,000, \$15,000-\$29,999, \$30,000-\$49,999, \$50,000-\$79,999, $\geq$ \$80,000, missing).

[†] In addition to age, sex, and baseline demographic factors, this model is further adjusted for the following baseline lifestyle and mental health factors: smoking (never, past, current, missing); alcohol intake (none- < 3 times per month, 1-3 times per week, 4+ times per week, missing); physical activity index (active, moderately active, inactive, missing); and life stress (not at all stressful, not very stressful, a bit stressful, quite a bit or extremely stressful, missing).

[‡] In addition to age, sex, baseline demographic, lifestyle, and mental health factors, this model is further adjusted for the following baseline dietary factors: consumption of sugar-sweetened beverages (yes, no); fruit and vegetable intake (times per day); sodium (mg per day); sugar (g per day); energy intake (kcal per day); and breakfast consumption (yes, no). This is the main model reported for this analysis.

[§] In addition to age, sex, and baseline demographic, lifestyle, mental health, and dietary factors, this model is further adjusted for the following baseline health conditions: high blood pressure (yes, no, missing); and diabetes (yes, no, missing).

[‖] In addition to age, sex, baseline demographic, lifestyle, mental health, and dietary factors, and baseline health conditions, this model is further adjusted for baseline BMI (kg/m^2, < 18.5, 18.5-24.9, 25-29.9, $\geq$ 30).

including date of immigration to or emigration from Canada. Therefore, we were unable to assess the relationship between eating frequency and timing and cases of CAD not requiring hospitalization or causing death, or censor CCHS 2.2 participants who emigrated from Canada during the follow-up period at the date of emigration. Fifth, the duration of follow-up was relatively short in the present study and may have presented insufficient incubation time for capturing hospitalization and mortality from CAD in this population. Therefore, whether associations exist between eating timing and frequency and CAD hospitalization and/or mortality in the longer-term is unknown.

Despite these limitations, our study has several strengths, including a prospective design, a large Canadian sample within a public healthcare system, a large sample of women (who have historically been underrepresented in epidemiologic and clinical CAD research[51,52]), exclusion of prevalent CAD, inclusion of a wide range of socioeconomic and health statuses, minimal missing data, and comprehensive assessment of various demographic, lifestyle, dietary, and health-related factors, which we were able to control for in our Cox regression models.

Future directions

The present study has analyzed the available Canadian data and identified that additional prospective cohort and clinically based longitudinal studies that enroll participants of diverse demographics are needed to confirm the findings of the present study and further elucidate these relationships at different age points. Although such studies are time- and resource-intensive, they are needed to elucidate potential mechanisms linking eating timing and frequency with hospitalization and/or mortality from CAD, and they also would enable the analysis of repeated measures of eating timing and frequency during the follow-up period. Future studies should attempt to capture usual eating timing and frequency repeatedly, in addition to food and nutrient intake, and they should explore the agreement and error associated with repeated measures of eating timing and frequency over time, as these have not yet been available to study in any dataset. Future studies of eating timing and frequency should attempt to account for other potential confounders and effect modifiers during follow-up time, such as bodyweight change, sedentary behaviour, shift work, circadian rhythms, light/dark exposure, and sleep pattern. An effort to link the CCHS 2.2 data with other population-based administrative health databases such as physician billing databases and insured patient registries also should be made to allow for the capture of cases of CAD that did not result in hospitalization and/or mortality. Future studies also should examine eating timing and frequency in relation to other cardiometabolic outcomes, such as hypertension, dyslipidemia, and stroke, which may have different etiologic pathways.

Conclusions

We observed in this population-based prospective longitudinal cohort study that consuming breakfast, between-meal consumptions, and eating 4-5 times per day are common eating patterns among Canadian adults and are linked to

higher socioeconomic status and a healthier lifestyle. We did not detect an association between eating timing and frequency (measured as skipping breakfast, between-meal consumption, and eating frequency) and risk of hospitalization and/or mortality from CAD in this population. However, the relationships between eating timing and frequency, and socioeconomic, demographic, lifestyle, and mental health factors are multi-directional and complex, and the direct associations between eating timing and frequency patterns and hospitalization and/or mortality from CAD may have been offset by the interplay of these factors. Replication in other long-term studies representing diversity in participant socio-demographic characteristics is needed, as are more repeated and validated assessments of usual eating timing and frequency in nutrition studies.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. GBD 2016 Mortality Collaborators. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1084-150.

2. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet 2015;386:2145-91.

3. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation 2020;141:e139-596.

4. Tarride JE, Lim M, DesMeules M, et al. A review of the cost of cardiovascular disease. Can J Cardiol 2009;25:e195-202.

5. Mendis S, Puska P, Norrving B. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization, 2011.

6. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155,722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet 2020;395:795-808.

7. GBC 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;393:1958-72.

8. St-Onge MP, Ard J, Baskin ML, et al. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation 2017;135:e96-121.

9. Kant AK, Graubard BI. Secular trends in patterns of self-reported food consumption of adult Americans: NHANES 1971-1975 to NHANES 1999-2002. Am J Clin Nutr 2006;84:1215-23.

10. Haines PS, Guilkey DK, Popkin BM. Trends in breakfast consumption of US adults between 1965 and 1991. J Am Diet Assoc 1996;96:464-70.

11. Piernas C, Popkin BM. Snacking increased among U.S. adults between 1977 and 2006. J Nutr 2010;140:325-32.

12. Barr SI, Vatanparast H, Smith J. Breakfast in Canada: prevalence of consumption, contribution to nutrient and food group intakes, and variability across tertiles of daily diet quality. A study from the International Breakfast Research Initiative. Nutrients 2018;10:985. correction 2020;12:2675.

13. Vatanparast H, Islam N, Patil RP, et al. Snack consumption patterns among Canadians. Nutrients 2019;11:1152.

14. Cummings DE, Purnell JQ, Frayo RS, et al. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001;50:1714-9.

15. Song WO, Chun OK, Obayashi S, Cho S, Chung CE. Is consumption of breakfast associated with body mass index in US adults? J Am Diet Assoc 2005;105:1373-82.

16. van der Heijden AA, Hu FB, Rimm EB, van Dam RM. A prospective study of breakfast consumption and weight gain among U.S. men. Obesity (Silver Spring) 2007;15:2463-9.

17. Mattes RD. Snacking: a cause for concern. Physiol Behav 2018;193:279-83.

18. Barnes TL, French SA, Harnack LJ, Mitchell NR, Wolfson J. Snacking behaviors, diet quality, and body mass index in a community sample of working adults. J Acad Nutr Diet 2015;115:1117-23.

19. Farshchi HR, Taylor MA, Macdonald IA. Deleterious effects of omitting breakfast on insulin sensitivity and fasting lipid profiles in healthy lean women. Am J Clin Nutr 2005;81:388-96.

20. Jenkins DJ, Wolever TM, Vuksan V, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. N Engl J Med 1989;321:929-34.

21. Stote KS, Baer DJ, Spears K, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. Am J Clin Nutr 2007;85:981-8.

22. Bi H, Gan Y, Yang C, et al. Breakfast skipping and the risk of type 2 diabetes: a meta-analysis of observational studies. Publ Health Nutr 2015;18:3013-9.

23. Arnason TG, Bowen MW, Mansell KD. Effects of intermittent fasting on health markers in those with type 2 diabetes: a pilot study. World J Diabetes 2017;8:154-64.

24. Varady KA, Bhutani S, Church EC, Klempel MC. Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults. Am J Clin Nutr 2009;90:1138-43.

25. Eshghinia S, Mohammadzadeh F. The effects of modified alternate-day fasting diet on weight loss and CAD risk factors in overweight and obese women. J Diabetes Metab Disord 2013;12:4.

26. Mattson MP, Allison DB, Fontana L, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A 2014;111:16647-53.

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Eating Timing/Frequency and Coronary Disease

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27. Ciobanu O, Sandu RE, Balseanu AT, et al. Caloric restriction stabilizes body weight and accelerates behavioral recovery in aged rats after focal ischemia. Aging Cell 2017;16:1394-403.

28. Freire R. Scientific evidence of diets for weight loss: different macronutrient composition, intermittent fasting, and popular diets. Nutrition 2020;69:110549.

29. Patterson RE, Sears DD. Metabolic effects of intermittent fasting. Annu Rev Nutr 2017;37:371-93.

30. Cahill LE, Chiuve SE, Mekary RA, et al. Prospective study of breakfast eating and incident coronary heart disease in a cohort of male US health professionals. Circulation 2013;128:337-43.

31. Kubota Y, Iso H, Sawada N, Tsugane S, Group JS. Association of breakfast intake with incident stroke and coronary heart disease: the Japan Public Health Center-Based Study. Stroke 2016;47:477-81.

32. Rong S, Snetselaar LG, Xu G, et al. Association of skipping breakfast with cardiovascular and all-cause mortality. J Am Coll Cardiol 2019;73: 2025-32.

33. Kakarmath SS, Zack RM, Leyna GH, et al. Dietary determinants of serum total cholesterol among middle-aged and older adults: a population-based cross-sectional study in Dar es Salaam, Tanzania. BMJ Open 2017;7:e015028.

34. Kim HN, Song SW. Associations between macronutrient intakes and obesity/metabolic risk phenotypes: findings of the Korean National Health and Nutrition Examination Survey. Nutrients 2019;11:628.

35. Bodén S, Myte R, Wennberg M, et al. The inflammatory potential of diet in determining cancer risk; a prospective investigation of two dietary pattern scores. PloS One 2019;14:e0214551.

36. Banna JC, McCrory MA, Fialkowski MK, Boushey C. Examining plausibility of self-reported energy intake data: considerations for method selection. Front Nutr 2017;4:45.

37. Garriguet D. Canadians' eating habits. Health Rep 2007;18:17-32.

38. Garriguet D. Overview of Canadians' eating habits. Available at: https://www150.statcan.gc.ca/n1/en/pub/82-620-m/82-620-m2006002-eng.pdf?st=XVKCYWez. Accessed June 16, 2022.

39. Leech RM, Worsley A, Timperio A, McNaughton SA. Characterizing eating patterns: a comparison of eating occasion definitions. Am J Clin Nutr 2015;102:1229-37.

40. Health Canada. Canadian Community Health Survey Cycle 2.2, Nutrition (2004) A Guide to Accessing and Interpreting the Data. Ottawa, ON: Health Canada, 2008.

41. Mekary RA, Giovannucci E, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. Am J Clin Nutr 2012;95:1182-9.

42. Mekary RA, Giovannucci E, Cahill L, et al. Eating patterns and type 2 diabetes risk in older women: breakfast consumption and eating frequency. Am J Clin Nutr 2013;98:436-43.

43. Kant AK. Eating patterns of US adults: meals, snacks, and time of eating. Physiol Behav 2018;193:270-8.

44. Siega-Riz AM, Popkin BM, Carson T. Differences in food patterns at breakfast by sociodemographic characteristics among a nationally representative sample of adults in the United States. Prev Med 2000;30: 415-24.

45. Si Hassen W, Castetbon K, Péneau S, et al. Socio-economic and demographic factors associated with snacking behavior in a large sample of French adults. Int J Behav Nutr Phys Act 2018;15:25.

46. Carew AS, Mekary RA, Kirkland S, et al. Prospective study of skipping meals to lose weight as a predictor of incident type 2 diabetes with potential modification by cardiometabolic risk factors: the Canadian 1995 Nova Scotia Health Survey. CanJ Diabetes 2021;45: 306-12.

47. Schultz WM, Kelli HM, Lisko JC, et al. Socioeconomic status and cardiovascular outcomes: challenges and interventions. Circulation 2018;137:2166-78.

48. Colpani V, Baena CP, Jaspers L, et al. Lifestyle factors, cardiovascular disease and all-cause mortality in middle-aged and elderly women: a systematic review and meta-analysis. Eur J Epidemiol 2018;33: 831-45.

49. Ofori-Asenso R, Owen AJ, Liew D. Skipping breakfast and the risk of cardiovascular disease and death: a systematic review of prospective cohort studies in primary prevention settings. J Cardiovasc Dev Dis 2019;6:30.

50. Public Health Agency of Canada. Heart Disease in Canada: Highlights from the Canadian Chronic Disease Surveillance System. Available at: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/heart-disease-fact-sheet/heart-disease-factsheet-eng.pdf. Accessed June 16, 2022.

51. Liu KA, Mager NA. Women's involvement in clinical trials: historical perspective and future implications. Pharm Pract (Granada) 2016;14: 708.

52. Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. JAMA Intern Med 2014;174: 1868-70.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.03.011.