

Meta-Analysis of Relation of Skipping Breakfast With Heart Disease



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To determine whether skipping breakfast is associated with heart disease, the first meta-analysis of currently available epidemiological studies was performed. To identify case-control, cross-sectional, longitudinal, or cohort studies investigating the association of skipping breakfast with prevalence, incidence, or mortality of heart disease in adults, PubMed, and Web of Science were searched through April 2019. Adjusted (if unavailable, unadjusted) hazard ratios (HRs) or odds ratios (ORs) with their confidence interval (CIs) of prevalence, incidence, or mortality for skipping breakfast were extracted from each study. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic HRs/ORs in the random-effects model. Eight eligible studies with a total of 284,484 participants were identified and included in the present meta-analysis. The primary meta-analysis combining HRs for Q1 (first quartile, most skipping breakfast) versus Q4 (fourth quartile, least skipping breakfast) from 3 studies together with other HRs/ORs demonstrated that skipping breakfast was associated with the significantly increased risk of heart disease (pooled HR/OR 1.24; 95% CI 1.09 to 1.40; $p = 0.001$). In sensitivity analyses combining HRs for Q2 (second quartile, second most skipping breakfast) versus Q4 or HRs for Q3 (third quartile, second least skipping breakfast) versus Q4 from 3 studies together with other HRs/ORs, the association of skipping breakfast with the increased risk of heart disease in the primary meta-analysis was confirmed. In conclusion, skipping breakfast is associated with the increased risk of heart disease. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:978–986)

Skipping breakfast is associated with cardiometabolic risk including metabolic risk profiles, overweight, obesity, hypertension, diabetes mellitus, and cardiovascular disease.¹ A recent systematic review² suggests the association of skipping breakfast with worse lipid profiles, blood pressure levels, insulin resistance, and metabolic syndrome. Large epidemiological studies reported that skipping breakfast was associated with the increased risk of type 2 diabetes mellitus in both females³ and males.⁴ Furthermore, a recent cross-sectional study⁵ provided the association of skipping breakfast with the increased risk of prevalent non-coronary and generalized atherosclerosis independently of conventional cardiovascular risk factors. However, the impact of skipping breakfast on the risk (i.e., prevalence, incidence, or mortality) of cardiovascular disease, especially heart disease, has been less investigated. In the present article, to determine whether skipping breakfast is

associated with heart disease, the first meta-analysis of currently available epidemiological studies was performed.

Methods

We conducted the present meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (<http://www.prisma-statement.org>). PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) and Web of Science (<http://www.webofknowledge.com/wos>) were searched through April 2019. Search terms included *breakfast*; *cardiac*, *cardiovascular*, *coronary artery*, *coronary heart*, *ischemic coronary*, or *ischemic heart*; and *disease*, *event*, *death*, or *mortality*. Studies meeting the following criteria were included in the present meta-analysis: the design was a case-control, cross-sectional, longitudinal, or cohort study; the study population was adults; the study investigated the association of skipping breakfast with prevalence, incidence, or mortality of heart disease including coronary artery disease (CAD).

Adjusted (if unavailable, unadjusted) hazard ratios (HRs) or odds ratios (ORs) with their confidence interval (CIs) of prevalence, incidence, or mortality for skipping breakfast were extracted from each study. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic HRs/ORs in the random-effects model. Funnel plot asymmetry (suggesting the presence of publication bias) was mathematically assessed using the linear regression test. All analyses were performed using

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See page 986 for disclosure information.

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Review Manager version 5.3 (<http://tech.cochrane.org/revman>) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey).

Results

As illustrated in [Supplementary Figure S1](#), 8 eligible studies^{6–13} with a total of 284,484 participants ([Table 1](#)) were identified and included in the present meta-analysis. Adjusted^{7,8,10–13} and unadjusted^{6,9} HRs/ORs were available in 6 and 2 studies respectively, and HRs^{6–8,10,11} and ORs^{9,12,13} were extracted in 5 and 3 studies, respectively ([Table 2](#)). Six studies^{7–10,12,13} reported HRs/ORs of acute coronary syndrome,⁹ CAD,^{10,12,13} coronary heart disease (CHD),⁷ or ischemic heart disease⁸; whereas, 2 studies^{6,11} provided HRs of heart disease. In 6 studies,^{6,7,9,10,12,13} HRs/ORs of disease incidence/prevalence were available; whereas, in 2 studies,^{8,11} HRs of disease mortality were extracted. In 3 studies,^{6,10,11} participants were divided quartiles (Q1 to Q4) according to the frequency of skipping breakfast: Q1, the most skipping; Q2, the second most skipping; Q3, the second least skipping; and Q4, the least skipping. In the primary meta-analysis, HRs for Q1 versus Q4 from the 3 studies^{6,10,11} were combined together with other HRs/ORs; whereas, in the sensitivity analyses, HRs for Q2 versus Q4 or HRs for Q3 versus Q4 from the 3 studies^{6,10,11} were combined together with other HRs/ORs ([Table 3](#)). Dissimilar relative risk estimates were also sequentially eliminated in sensitivity analyses ([Table 3](#)).

The primary meta-analysis demonstrated that skipping breakfast was associated with the significantly increased risk of heart disease (pooled HR/OR 1.24; 95% CI 1.09 to 1.40; $p = 0.001$; [Figure 1](#)). In the sensitivity analysis I, combining HRs for Q2 versus Q4 (instead of HRs for Q1 versus Q4 in the primary meta-analysis) from the 3 studies^{6,10,11} together with other HRs/ORs brought about the significant disadvantage of skipping breakfast (pooled HR/OR 1.21; $p = 0.002$; [Figure 2](#)). The sensitivity analysis II combining HRs for Q3 versus Q4 (instead of HRs for Q1 versus Q4 in the primary meta-analysis) from the 3 studies^{6,10,11} together with other HRs/ORs created the significant drawback of skipping breakfast (pooled HR/OR 1.20; $p = 0.006$; [Figure 3](#)). In the sensitivity analysis III, combining adjusted HRs/ORs^{7,8,10–13} (excluding unadjusted HRs/ORs^{6,9}) resulted in the significant disadvantage of skipping breakfast (pooled HR/OR 1.19; $p = 0.01$; [Figure 4](#)). The sensitivity analysis IV combining HRs^{6–8,10,11} (excluding ORs^{9,12,13}) generated the significant drawback of skipping breakfast (pooled OR 1.25; $p = 0.01$; [Figure 5](#)). In the sensitivity analysis V, combining HRs/ORs of acute coronary syndrome/CAD/CHD/ischemic heart disease^{7–10,12,13} (excluding HRs of heart disease^{6,11}) led to the significant disadvantage of skipping breakfast (pooled HR/OR 1.20; $p = 0.01$; [Figure 6](#)). The sensitivity analysis VI combining HRs/ORs of disease incidence/prevalence^{6,7,9,10,12,13} (excluding HRs of disease mortality^{8,11}) produced the significant drawback of skipping breakfast (pooled HR/OR 1.18; $p = 0.01$; [Figure 7](#)).

Significant funnel plot asymmetry for the primary meta-analysis ($p = 0.04$) was identified ([Figure 7](#)), which suggested the presence of publication bias. Hence, another

Study	Reference number	Design	Region	Database	Inclusion criteria		Patient number	Age (years)*	Male (%)	Follow-up
					Age (years)	Participants				
Byrne 2016	6	Prospective cohort	US	Employee wellness program	Unavailable	University employees	10,248	41.2 ± 10.8	31.9	2–10 years
Cahill 2013	7	Prospective cohort	US	HPFS	40–75	Male health professionals	26,902	58.6	100	387,954 person-years
Iso 2007	8	Prospective cohort	Japan	JACC	40–79	General population	108,063	Unavailable	42.1	1,373,855 person-years
Konidari 2014	9	Case control [†]	Greece	Major general hospitals	Unavailable	Case: First ACS event; Control: Free from CVD	500	60 ± 12	83.2	None
Kubota 2016	10	Prospective cohort	Japan	JPHC study	40–69	Free from stroke, MI, AP, or cancer	82,772	56.5	46.7	1,050,030 person-years
Rong 2019	11	Prospective cohort	US	NHANES III	40–75	Free from CVD or cancer	6550	53.2 ± 0.3[SE]	48.0	Median, 112,148 person-years
Sharma 2018	12	Case control	India	Tertiary cardiac care hospital	> 18	Case: CAD; control: free from CAD	1607	Unavailable	85.7	None
Tada 2018	13	Cross sectional	Japan	Specific health checkups	> 40	General population	47,842	71.4 ± 11.0	35.4	None

ACS = acute coronary syndrome; AP = angina pectoris; CAD = coronary artery disease; CVD = cardiovascular disease; HPFS = Health Professionals Follow-up Study; JACC = Japan Collaborative Cohort Study for Evaluation of Cancer; JPHC = Japan Public Health Center-Based Prospective; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey; SE = standard error.

* Mean or mean ± standard deviation.

[†] Age and sex matched.

Table 2
Relative risk estimates for skipping breakfast

Study	Reference number	Outcomes		Adjustment	Relative risk estimates (95% confidence intervals) for skipping breakfast			
		Disease	Definition					
Byrne 2016	6	Heart disease*	Yearly health risk assessment	Undone	HR for seldom or never eating: Reference	HR for 2-3 times/week eating: 0.89 (0.61-1.31)	HR for most mornings eating: 1.02 (0.71-1.45)	HR for every day eating: 0.71 (0.53-0.98)
Byrne 2016	6	Heart disease*	Yearly health risk assessment	Undone	HR for seldom or never eating: 1.39 (1.02-1.89) ^{†,¶}	HR for 2-3 times/week eating: 1.24 (0.76-2.03) ^{‡,¶}	HR for most mornings eating: 1.41 (0.88-2.26) ^{§,¶}	HR for every day eating: Reference
Cahill 2013	7	CHD [‡]	Each biennial questionnaire, confirmed by review of medical records and autopsy reports	Age, diet, demographic, and activity factors; and BMI, DM, HT, and hypercholesterolemia, updated every 2 years	HR for not eating breakfast: 1.18 (0.98-1.43) ^{†,‡,§}			
Iso 2007	8	IHD**	Death certificates in each area, ICD-9/10	Age and area of study	HR for cutting breakfast in females: 1.32 (0.66-2.67) ^{†,‡,§}		HR for cutting breakfast in males: 1.90 (1.13-3.19) ^{†,‡,§}	
Konidari 2014	9	ACS ^{††}	Blood tests for AMI, occurrence of ≥1 angina episodes at rest within preceding 48 hours for UA	Undone	OR for <5 times/week: 1.84 (0.97-3.50)			
Kubota 2016	10	CHD [‡]	Medical records of Hospitals in 9 PHC areas	Age, sex, ethanol, energy, vegetables, fruits, fish, soy, milk/dairy products, nuts, saturated fatty acid, dietary fiber, sodium intake, smoking status, leisure-time sports, sleep duration, perceived mental stress, living alone, physical labor, and public health center area	HR for 0-2 times/week eating: 0.96 (0.73-1.25) [†]	HR for 3-4 times/week eating: 1.27 (0.87-1.85) [†]	HR for 5-6 times/week eating: 0.95 (0.62-1.44) [§]	HR for 7 times/week eating: Reference
Rong 2019	11	Heart disease ^{‡‡}	NHANES III Public-Use Linked Mortality File, ICD-9/10	Age, sex, race/ethnicity, marital status, family income level, smoking status, alcohol intake, physical activity, total energy intake, overall diet quality indicated by Healthy Eating Index-2010, BMI, HT, DM, and dyslipidemia	HR for never eating: 1.59 (0.90-2.80) [†]	HR for rarely eating: 1.22 (0.72-2.08) [‡]	HR for some days eating: 0.90 (0.61-1.34) [§]	HR for every day eating: reference
Sharma 2018	12	CAD ^{§§}	Angiography	Done but unavailable covariates	OR for breakfast skippers (eating breakfast ≤ 2 times/week): 1.348 (1.076-1.689) ^{†,‡,§}			
Tada 2018	13	CAD ^{§§}	Self-reports	Variables with p < 0.10 on univariate analyses (essentially, almost all of the variables)	OR for skipping breakfast >3 times/week: 1.06 (0.91-1.24) ^{†,‡,§}			

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMI = body mass index; CAD = coronary artery disease; CHD = coronary heart disease; DM = diabetes mellitus; HR = hazard ratio; HT = hypertension; ICD-9/10 = 9th/10th Revision International Statistical Classification of Diseases; IHD = ischemic heart disease; N/A = not available; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PHC = Public Health Center; UA = unstable angina.

* Heart disease incidence.

[†] Pooled in the primary meta-analysis (q.v. text and Table 3).

[‡] Pooled in the sensitivity analysis-I (q.v. text and Table 3).

[§] Pooled in the sensitivity analysis-II (q.v. text and Table 3).

[¶] Calculated by us from the above-mentioned HRs using the standard formulae.

^{‡‡} CHD incidence.

** IHD mortality.

^{††} ACS prevalence.

^{‡‡} Heart disease mortality.

^{§§} CAD prevalence.

Table 3
 Combined relative risk estimates in the primary meta-analysis and the sensitivity analyses

Study	Reference number	Relative risk estimates for skipping breakfast					Primary meta-analysis Combining HRs for Q1 vs Q4 together with other HRs/ORs	Sensitivity analysis I Combining HRs for Q2 vs Q4 together with other HRs/ORs	Sensitivity analysis II Combining HRs for Q3 vs Q4 together with other HRs/ORs	Sensitivity analysis III Combining adjusted HRs/ORs (excluding unadjusted HRs/ORs)	Sensitivity analysis IV Combining HRs from prospective cohort studies (excluding ORs)	Sensitivity analysis V Combining HRs/ORs of ACS/CAD/CHD/IHD (excluding HRs of heart disease)	Sensitivity analysis VI Combining HRs/ORs of disease incidence/prevalence (excluding HRs of disease mortality)
Byrne 2016	6	Unadjusted	HR	of heart disease incidence	for Q1 vs Q4	✓				✓		✓	
Byrne 2016	6	Unadjusted	HR	of heart disease incidence	for Q2 vs Q4		✓						
Byrne 2016	6	Unadjusted	HR	of heart disease incidence	for Q3 vs Q4			✓					
Cahill 2013	7	Adjusted	HR	of CHD incidence		✓	✓	✓	✓	✓	✓	✓	
Iso 2007	8	Adjusted	HR	of IHD mortality in females		✓	✓	✓	✓	✓	✓		
Iso 2007	8	Adjusted	HR	of IHD mortality in males		✓	✓	✓	✓	✓	✓		
Konidari 2014	9	Unadjusted	OR	of ACS prevalence		✓	✓	✓			✓	✓	
Kubota 2016	10	Adjusted	HR	of CAD incidence	for Q1 vs Q4	✓			✓	✓	✓	✓	
Kubota 2016	10	Adjusted	HR	of CAD incidence	for Q2 vs Q4		✓						
Kubota 2016	10	Adjusted	HR	of CAD incidence	for Q3 vs Q4			✓					
Rong 2019	11	Adjusted	HR	of heart disease mortality	for Q1 vs Q4	✓			✓	✓			
Rong 2019	11	Adjusted	HR	of heart disease mortality	for Q2 vs Q4		✓						
Rong 2019	11	Adjusted	HR	of heart disease mortality	for Q3 vs Q4			✓					
Sharma 2018	12	Adjusted	OR	of CAD prevalence		✓	✓	✓	✓		✓	✓	
Tada 2018	13	Adjusted	OR	of CAD prevalence		✓	✓	✓	✓		✓	✓	

✓ = included; ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = coronary heart disease; HR = hazard ratio; IHD = ischemic heart disease; OR = odds ratio; Q1 = quartile of the most skipping breakfast; Q2 = quartile of the second most skipping breakfast; Q3 = quartile of the second least skipping breakfast; Q4 = quartile of the least skipping breakfast.

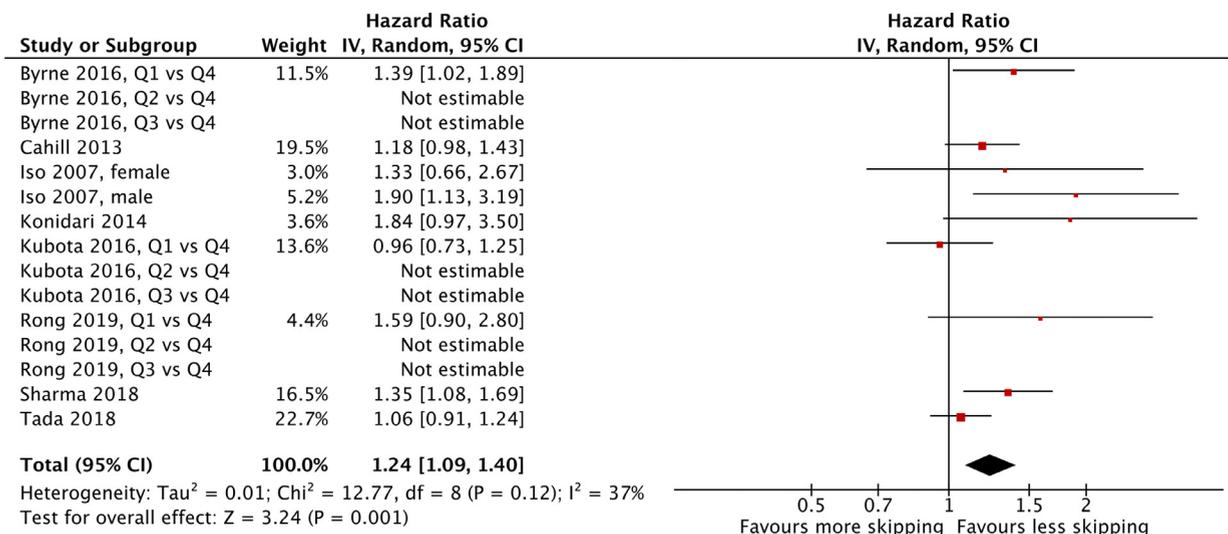


Figure 1. Primary meta-analysis combining hazard ratios for Q1 versus Q4 from the 3 studies^{6,10,11} together with other hazard/odds ratios (Table 3). CI=confidence interval; IV=inverse variance; Q1=first quartile (most skipping breakfast); Q2=second quartile (second most skipping breakfast); Q3=third quartile (second least skipping breakfast); and Q4=fourth quartile (least skipping breakfast).

sensitivity analysis was performed using the trim and fill method,¹⁴ which conservatively imputes hypothetical negative unpublished studies to mirror the positive identified published studies causing funnel plot asymmetry. The imputed hypothetical studies generated symmetrical funnel plot, and the pooled analysis integrating both the identified published and hypothetical unpublished studies continued to indicate the association of skipping breakfast with the significantly increased risk of heart disease (pooled HR/OR 1.17; 95% CI 1.02 to 1.34; p=0.03; Figure 7).

Restricted maximum likelihood meta-regression of the primary meta-analysis demonstrated no significant differences in the study design (p=0.44; Supplementary Figure S2) and region (p=0.37; Supplementary Figure S3).

Discussion

The present meta-analysis suggests that skipping breakfast is associated with the increased risk of heart disease, which was valid in sensitivity analyses. A number of physiological mechanisms could explain the present findings. First, skipping breakfast causes hunger sensation and bring about overeating later in the day, which may result in overweight and insulin resistance, elevate blood pressure levels owing to overactivity of the hypothalamic-pituitary-adrenal axis, and deleteriously alter lipid levels.¹⁴ Second, rather than one of causes for metabolic changes, skipping breakfast may be one of behavioral markers for insalubrious dietary patterns and unhealthy lifestyle habits such as poor

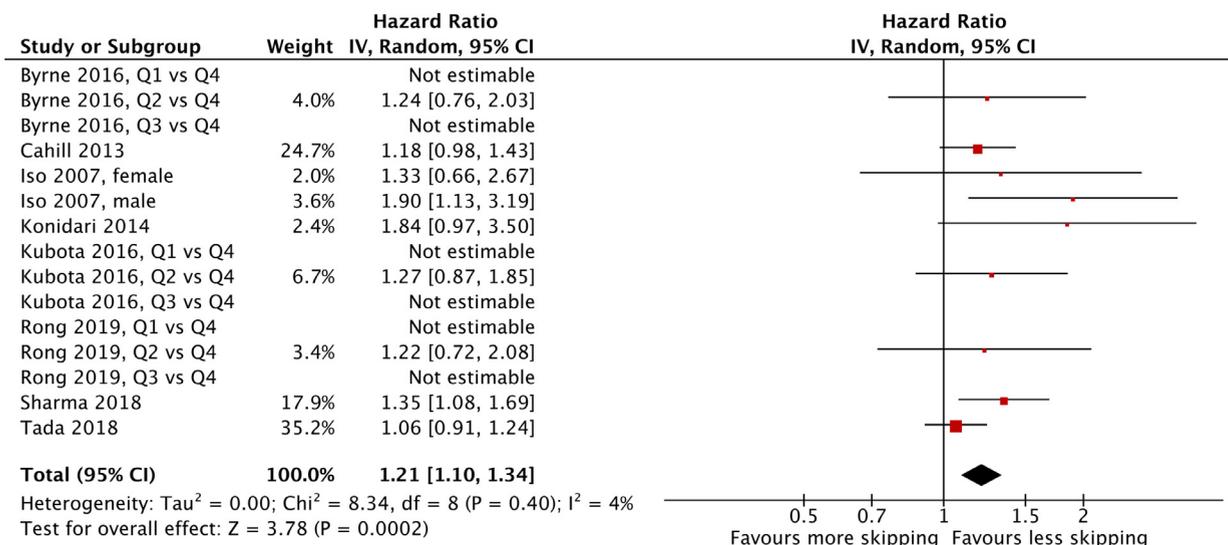


Figure 2. Sensitivity analysis I combining hazard ratios for Q2 versus Q4 from the 3 studies^{6,10,11} together with other hazard/odds ratios (Table 3). CI=confidence interval; IV=inverse variance; Q1=first quartile (most skipping breakfast); Q2=second quartile (second most skipping breakfast); Q3=third quartile (second least skipping breakfast); and Q4=fourth quartile (least skipping breakfast).

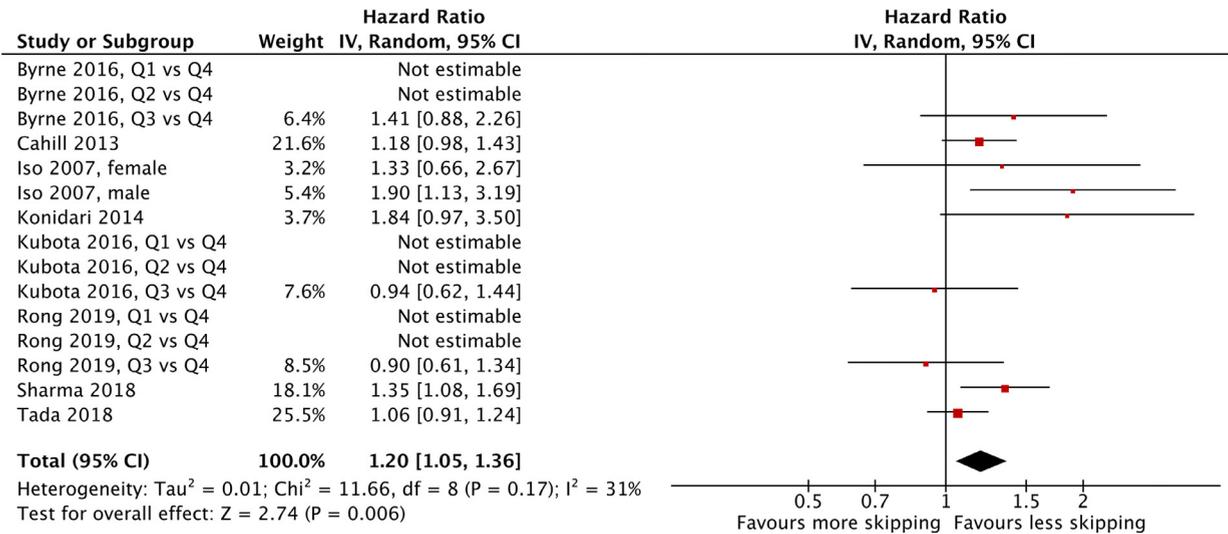


Figure 3. Sensitivity analysis II combining hazard ratios for Q3 versus Q4 from the 3 studies^{6,10,11} together with other hazard/odds ratios (Table 3). CI = confidence interval; IV = inverse variance; Q1 = first quartile (most skipping breakfast); Q2 = second quartile (second most skipping breakfast); Q3 = third quartile (second least skipping breakfast); and Q4 = fourth quartile (least skipping breakfast).

physical activity and somniphany.^{14–16} Third, the wide extent of psychological, socioeconomic, physical (built-environmental), political, and cultural factors may promote or suppress the frequency of eating breakfast, even after adjustment for a number of dietary and lifestyle factors such as smoking, alcohol intake, physical activity levels, total energy intake, and overall diet quality.¹⁴ The following potential molecular mechanism also may partially explain skipping breakfast associated cardiometabolic risk subsequently inducing cardiovascular disease. A delayed first active-phase meal protocol as a breakfast-skipping model in rats indicated the delay of (1) circadian oscillation of hepatic clock, (2) de novo fatty-acid synthesis genes, and (3) peaks of serum insulin, a synchronizer for the liver clock, bile acids, and nonesterified fatty acid.¹⁷ Furthermore, children and adolescents skipping breakfast are at

higher risk to be or suffer overweight and obesity,² and skipping breakfast appears associated with the presence of metabolic syndrome³ and type 2 diabetes mellitus,^{3,4} which may also explain the present results.

A few studies have investigated the association of skipping breakfast and stroke. A large (47,842 participants) cross-sectional study¹³ demonstrated no association of skipping breakfast with the prevalence of stroke (adjusted OR for >3 times skipping breakfast, 0.99; 95% CI 0.82 to 1.20; p = 0.928), whereas a large (82,772 participants) prospective cohort study¹⁰ indicated that skipping breakfast was associated with the increased incidence of stroke (adjusted HR for 0 to 2 vs 7 times/week eating 1.18; 95% CI 1.04 to 1.34; p = 0.01). The latter finding may be derived from the association of skipping breakfast with the increased incidence of cerebral hemorrhage (adjusted HR for 0 to 2 vs

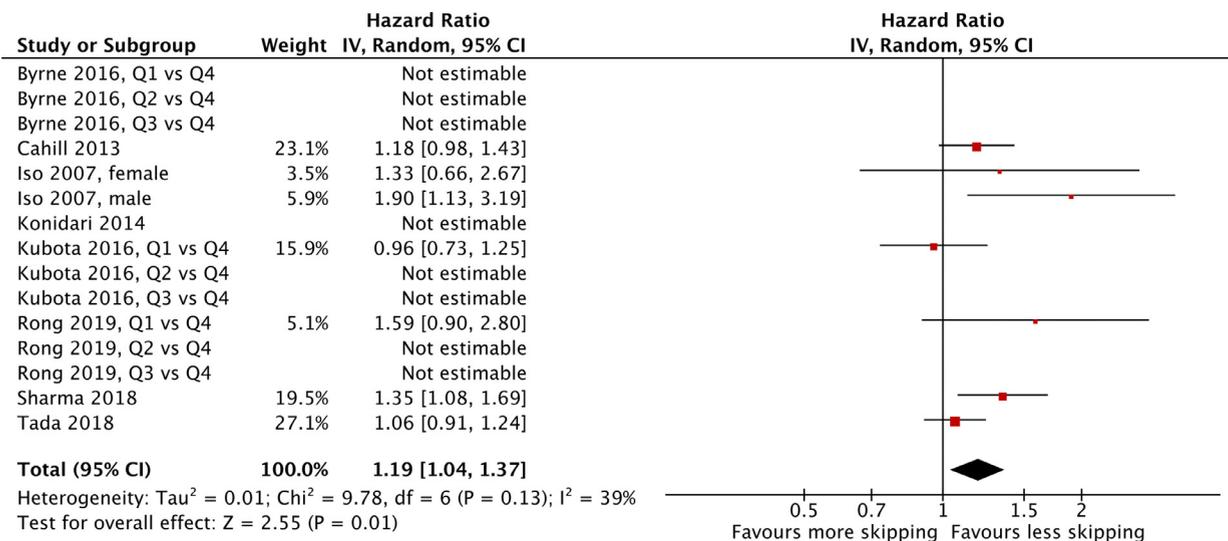


Figure 4. Sensitivity analysis III combining adjusted hazard/odds ratios^{7,8,10–13} (excluding unadjusted hazard/odds ratios^{6,9}) (Table 3). CI = confidence interval; IV = inverse variance; Q1 = first quartile (most skipping breakfast); Q2 = second quartile (second most skipping breakfast); Q3 = third quartile (second least skipping breakfast); and Q4 = fourth quartile (least skipping breakfast).

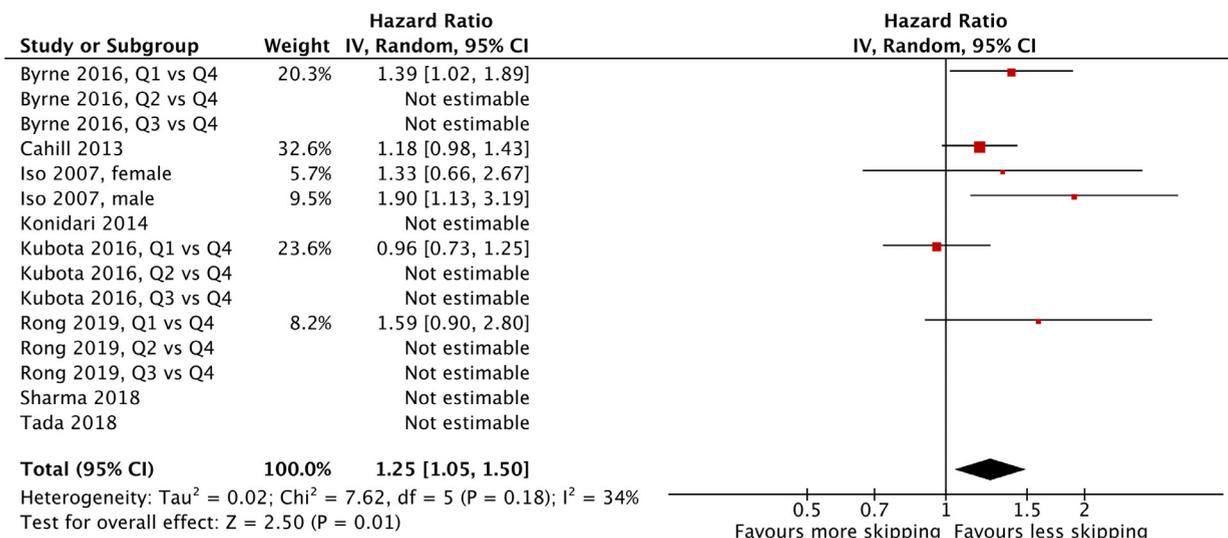


Figure 5. Sensitivity analysis IV combining hazard ratios^{6-8,10,11} (excluding odds ratios^{9,12,13}) (Table 3). CI = confidence interval; IV = inverse variance; Q1 = first quartile (most skipping breakfast); Q2 = second quartile (second most skipping breakfast); Q3 = third quartile (second least skipping breakfast); and Q4 = fourth quartile (least skipping breakfast).

7 times/week eating 1.36; 95% CI 1.10 to 1.70; p = 0.005), and no association of skipping breakfast with the increased cerebral infarction was identified (adjusted HR for 0 to 2 vs 7 times/week eating 1.10; 95% CI 0.92 to 1.30; p = 0.31). In the latter study,¹⁰ no association of skipping breakfast with the incidence of CHD was also demonstrated (adjusted HR for 0 to 2 vs 7 times/week eating 0.96; 95% CI 0.73 to 1.25; p = 0.75). Further researches would be required to confirm the present results between skipping breakfast and heart disease and to inspect the previous inconsistent findings^{10,13} between skipping breakfast and stroke.

The present findings should be construed with caution due to the following limitations. There was some notable qualitative heterogeneity in the studies included in

the present meta-analysis as above-mentioned in the results section. All the sensitivity analyses carefully and sequentially eliminating dissimilar relative risk estimates; however, confirmed the association of skipping breakfast with the increased risk of heart disease in the primary meta-analysis. Publication bias disfavoring skipping breakfast may affect the present results. Although the present mathematical assessment of the funnel plot detected significant asymmetry (suggesting the presence of publication bias), even adjusting for the asymmetry using the trim and fill method¹⁴ confirmed the findings of the primary meta-analysis.

In conclusion, skipping breakfast is associated with the increased risk of heart disease.

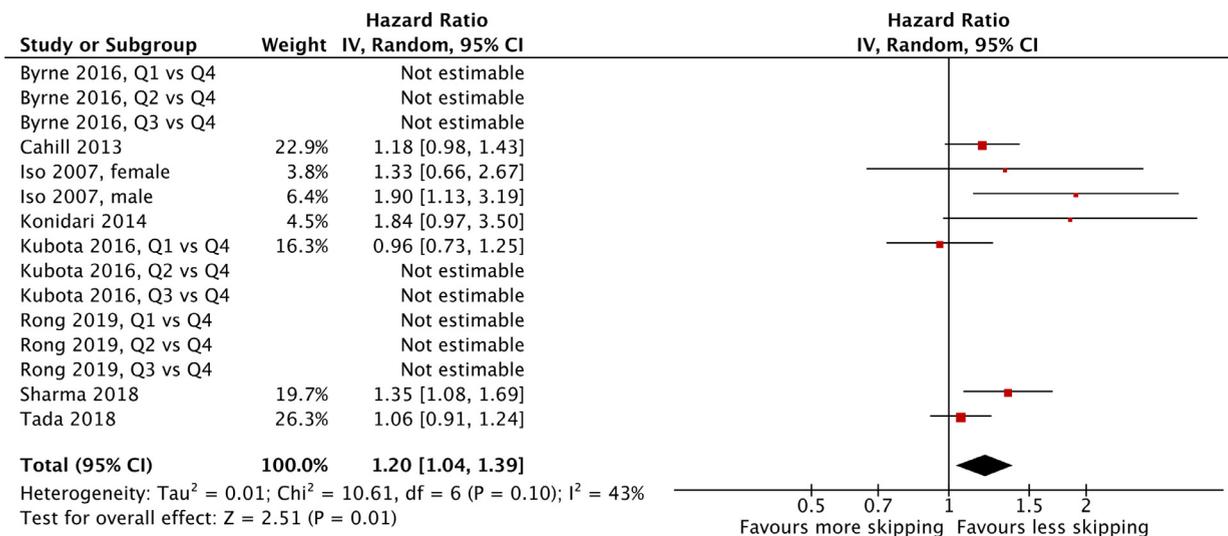


Figure 6. Sensitivity analysis V combining hazard/odds ratios of acute coronary syndrome, coronary artery disease, coronary heart disease, and ischemic heart disease^{7-10,12,13} (excluding hazard ratios of heart disease^{6,11}) (Table 3). CI = confidence interval; IV = inverse variance; Q1 = first quartile (most skipping breakfast); Q2 = second quartile (second most skipping breakfast); Q3 = third quartile (second least skipping breakfast); and Q4 = fourth quartile (least skipping breakfast).

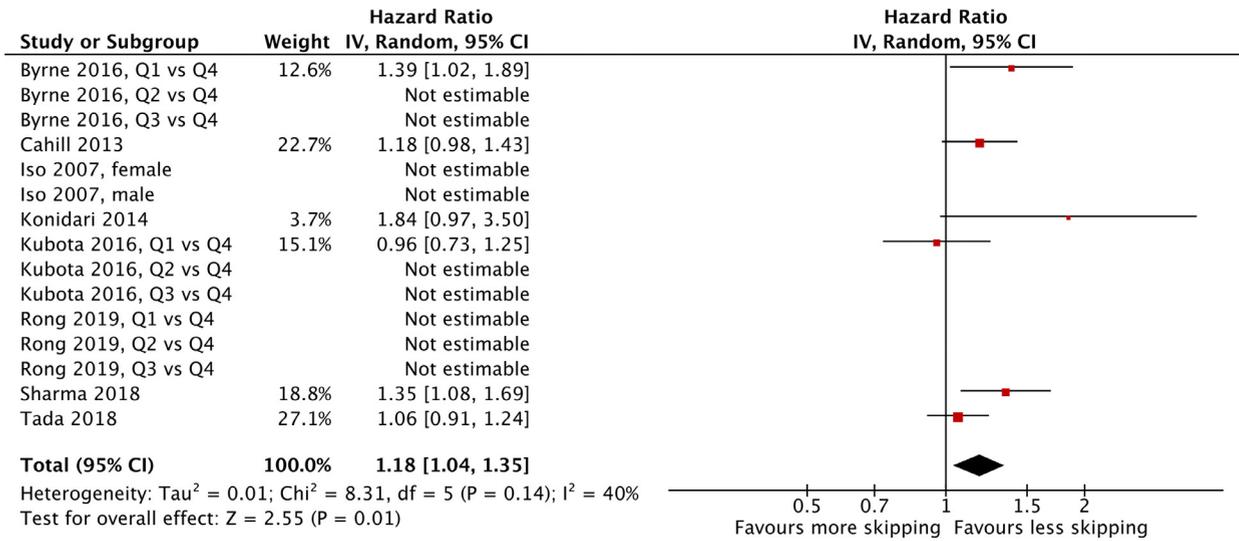


Figure 7. Sensitivity analysis V combining hazard/odds ratios of disease incidence/prevalence^{6,7,9,10,12,13} (excluding hazard ratios of disease mortality^{8,11}) (Table 3). CI = confidence interval; IV = inverse variance; Q1 = first quartile (most skipping breakfast); Q2 = second quartile (second most skipping breakfast); Q3 = third quartile (second least skipping breakfast); and Q4 = fourth quartile (least skipping breakfast).

Funnel Plot of Precision by Log hazard ratio

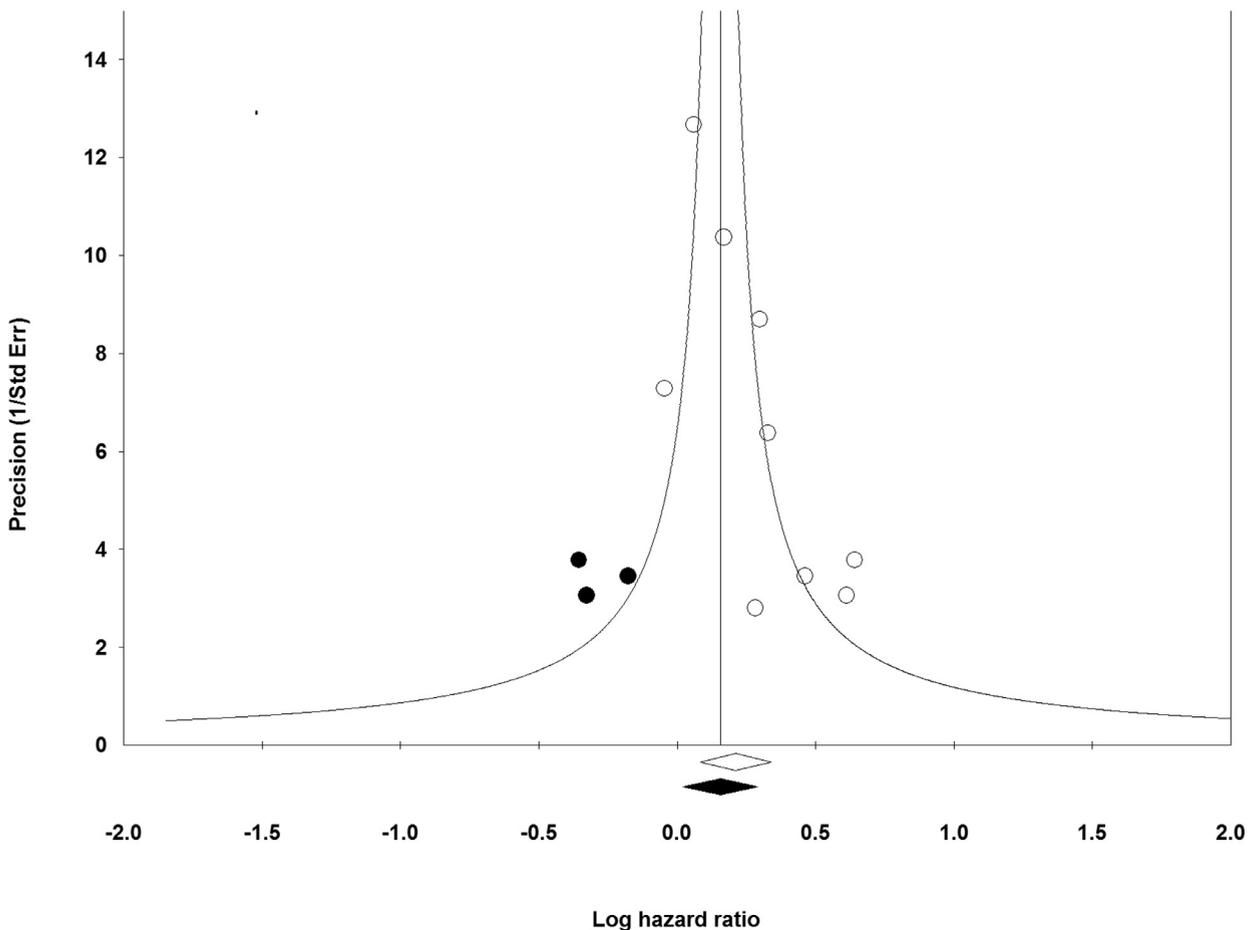


Figure 8. Funnel plot of precisions by logarithmic hazard/odds ratios of heart disease for skipping breakfast in the primary meta-analysis. Open and closed circles denote identified published and hypothetical unpublished studies, respectively. An open and closed lozenge denotes respectively an unadjusted summary estimate exclusively combining the identified published studies and an adjusted summary estimate integrating both the identified published and hypothetical unpublished studies.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.amjcard.2019.06.016.

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