SUPPLEMENTAL MATERIAL

Dugani et al., Risk factors for premature myocardial infarction: A systematic review and meta–analysis of 77 studies

Online Supplemental Material

Apo: apolipoprotein; BMI: body-mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; SD: standard deviation

Supplemental Table 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental Table 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7; Supplemental Method 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplemental Table 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supplemental Method1 ; Supplemental Table 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9; Supplemental Method 1; Supplemental Tables 3, 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Supplemental Tables 7-14; Supplemental Figures 1-14
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	34
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplemental Table 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplemental Tables 3, 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplemental Tables 6-14; Supplemental Figures 1-14
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	10-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	35; Supplemental Method 1; Supplemental Tables 3, 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplemental Tables 6-14; Supplemental Figures 1-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-19

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Supplemental Table 2: Search strategy

Medline; 1946-Present
Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®

ID	Searches
1	exp Myocardial Infarction/
2	acute coronary syndrome/
3	(AMI or MI or STEMI or NSTEMI).tw,kf.
4	((heart or coronary or cardiovasc* or cardiac* or myocard*) adj3 (attack* or infarc*)).tw,kf.
5	(acute adj2 coronary adj2 syndrome).tw,kf.
6	Young Adult/
7	Adult/
8	middle aged.sh.
9	adult.mp.
10	((early or premature or pre-mature or young* or earliest or earlier) adj2 (MI or (myocardial adj2 infarc*) or (heart adj2 attack*))).tw,kf.
11	(early or young* or premature* or earlie* or youth or untimely or oversoon).tw,kf.
12	or/1-5 [MI MeSH headings and textwords]
13	or/6-9 [Adults MeSH and textwords]
14	12 and 13 [MI AND Adults]
15	14 and 11 [MI AND Adults AND premature concept textwords]
16	15 or 10 [(MI AND Adults AND premature concept textwords) OR Premature NEAR MI]
17	exp Animals/ not (Humans/ and exp Animals/)
18	16 not 17 [Remove animal studies]
19	limit 18 to english language

Abbreviations: AMI: acute MI; MI: myocardial infarction; NSTEMI: non ST-elevation MI; STEMI: ST-elevation MI

EMBASE; 1947 to present

ID	Searches
1	heart infarction/ or acute heart infarction/ or anterior myocardial infarction/ or dressler syndrome/ or exp experimental myocardial infarction/ or heart atrium infarction/ or heart reinfarction/ or exp heart ventricle infarction/ or impending heart infarction/ or inferior myocardial infarction/ or non st segment elevation myocardial infarction/ or posterior myocardial infarction/ or silent myocardial infarction/ or st segment elevation myocardial infarction/
2	acute coronary syndrome/
3	(AMI or MI or STEMI or NSTEMI).tw,kw.
4	((heart or coronary or cardiovasc* or cardiac* or myocard*) adj2 (attack* or infarc*)).tw,kw.
5	(acute adj1 coronary adj2 syndrome).tw,kw.
6	young adult/ or adult/
7	middle aged/
8	((early or premature or pre-mature or young* or earliest or earlier) adj2 (MI or (myocardial adj2 infarc*) or (heart adj2 attack*))).tw.
9	(early or young* or premature* or earlie* or youth or untimely or oversoon).tw,kw.
10	or/1-5 [MI EMTREE and textwords]
11	or/6-7 [Age]
12	(exp animal/ or nonhuman/) not exp human/
13	10 and 11 [MI AND Age]
14	13 and 9 [MI AND Age AND premature concept textwords]
15	14 or 8 [(MI AND Adults AND premature concept textwords) OR Premature NEAR MI]
16	15 not 12 [Remove animal studies]
17	limit 16 to english language

Abbreviations: AMI: acute MI; MI: myocardial infarction; NSTEMI: non ST-elevation MI; STEMI: ST-elevation MI

EBSCO CINAHL

ID	Search Terms
S14	S11 OR S12
S13	S11 OR S12
S12	(young or premature or early) N2 (MI or myocardial or infarction)
S11	S9 AND S10
S10	TI (early or young* or premature* or earlie* or youth or untimely or oversoon) OR AB (early or young* or premature* or earlie* or youth or untimely or oversoon)
S9	S7 AND S8
S8	S5 OR S6
S7	S1 OR S2 OR S3 OR S4
S6	TI adult* OR AB adult*
S5	(MH "Young Adult") OR (MH "Middle Age") OR (MH "Adult")
S4	TI (acute N2 coronary) N2 syndrome OR AB (acute N2 coronary) N2 syndrome
S3	TI ((heart or coronary or cardiovasc* or cardiac* or myocard*) N2 (attack* or infarc*)) OR AB ((heart or coronary or cardiovasc* or cardiac* or myocard*) N2 (attack* or infarc*))
S2	TI (AMI or MI or STEMI or NSTEM) OR AB (AMI or MI or STEMI or NSTEM)
S1	(MH "Myocardial Infarction") OR (MH "Acute Coronary Syndrome")

Abbreviations: AMI: acute MI; MI: myocardial infarction; NSTEMI: non ST-elevation MI; STEMI: ST-elevation MI

Cochrane CENTRAL

ID	Search Terms
1	MeSH descriptor: [Acute Coronary Syndrome] this term only
2	AMI or MI or STEMI or NSTEMI
3	(heart or coronary or cardiovasc* or cardiac* or myocard*) near/3 (attack* or infarc*)
4	MeSH descriptor: [Myocardial Infarction] 1 tree(s) exploded
5	(acute near/2 coronary) near/3 syndrome
6	MeSH descriptor: [Young Adult] this term only
7	MeSH descriptor: [Adult] this term only
8	MeSH descriptor: [Middle Aged] this term only
9	(early or premature or pre-mature or young* or earliest or earlier) near/3 (MI or (myocardial near/2 infarc*) or (heart near/2 attack*))
10	early or young* or premature* or earlie* or youth or untimely or oversoon
11	#1 or #2 or #3 or #4 or #5
12	#6 or #7 or #8
13	#11 and #12
14	#13 or #9
15	#10 and #14 in Trials

Abbreviations: AMI: acute MI; MI: myocardial infarction; NSTEMI: non ST-elevation MI; STEMI: ST-elevation MI

Supplemental Method 1: Risk of Bias Assessment based on Newcastle-Ottawa Scale

Newcastle-Ottawa Quality Assessment Scale (Case Control Studies)

Selection

1) Is the case (i.e., premature MI) definition adequate?
   a) yes, with independent validation (low risk of bias)
   b) yes, e.g. record linkage or based on self-reports (low risk of bias)
   c) no description (unclear risk of bias)
2) Representativeness of premature MI cases
   a) consecutive or obviously representative series of premature MI (low risk of bias)
   b) potential for selection biases (high risk of bias)
   c) not stated (unclear risk of bias)
3) Selection of Controls
   a) hospital controls (low risk of bias)
   b) community controls (low risk of bias)
   c) no description provided (unclear risk of bias)
4) Definition of Controls
   a) no history of premature MI based on record or self-report (low risk of bias)
   b) no description of source (unclear risk of bias)

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for age (low risk of bias)
   b) study controls for ≥1 risk factors in risk models (low risk of bias)
   c) consider low-quality if not adjusted (high risk of bias)

Exposure

1) Ascertainment of exposure
   a) secure record (e.g. surgical records) (low risk of bias)
   b) structured interview where blind to case/control status (high risk of bias)
   c) interview not blinded to case/control status (high risk of bias)
   d) written self-report (high risk of bias)
   e) or medical record only (low risk of bias)
   f) no description (unclear risk of bias)
2) Same method of ascertainment for cases and controls
   a) yes (low risk of bias)
   b) no (high risk of bias)
   c) not reported (unclear risk of bias)
3) Non-Response rate
   a) same rate for both groups (low risk of bias)
   b) non respondents described (low risk of bias)
   c) rate different and no designation (high risk of bias)

Newcastle-Ottawa Quality Assessment Scale (Cohort Studies)

Selection

1) Representativeness of study population
   a) truly representative of average individual in the community (low risk of bias)
   b) somewhat representative of average individual in the community (low risk of bias)
   c) selected group of users e.g. nurses, volunteers (high risk of bias)
   d) no description of the derivation of the cohort (unclear risk of bias)
2) Selection of the non-exposed participants
   a) drawn from the same community as the exposed cohort (low risk of bias)
   b) drawn from a different source (high risk of bias)
   c) no description of the derivation of the non exposed cohort (unclear risk of bias)
3) Ascertainment of exposure
   a) secure record (e.g. medical records) (low risk of bias)
   b) structured interview (high risk of bias)
   c) written self-report (high risk of bias)
   e) no description (unclear risk of bias)
4) Demonstration that outcome of interest (i.e., premature MI) was not present at start of study
   a) yes (low risk of bias)
   b) no (unclear risk of bias)

Comparability

1) Comparability of cohorts on the basis of the analysis
   a) study controls for age (low risk of bias)
   b) study controls for ≥ 1 risk factors in risk models (high risk of bias)

Outcome

1) Assessment of outcome
   a) independent blind assessment (low risk of bias)
   b) record linkage (i.e., ICD codes) (low risk of bias)
   c) self-report (high risk of bias)
   d) no description (unclear risk of bias)
2) Was follow-up long enough (i.e., at least12 months) for outcome to occur?
   a) yes (low risk of bias)
   b) no (high risk of bias)
   c) Not reported (unclear risk of bias)
3) Adequacy of follow up of cohorts
   a) complete follow up- all subjects accounted for (low risk of bias)
   b) subjects lost to follow up unlikely to introduce bias- small number lost- >80 % follow up, or description provided of those lost) (low risk of bias)
   c) follow up rate < 80% and no description of those lost (high risk of bias)
   d) no statement (unclear risk of bias)

Supplemental Table 3: Risk of bias assessment for each risk factor from individual studies

Result reported	Risk factor	Risk factor ascertainment	Risk of Bias
frequency	smoking	self-reported	high
	family history of cardiac disease		
	alcohol use		
	clinical risk factor (e.g., diabetes, hypertension)		
frequency	race	self-reported	moderate
	clinical risk factor (e.g., diabetes, hypertension)	verified (measuring HbA1c, blood pressure, lipids, or if on medicines for these conditions)	
Result reported	**Risk factor ascertainment**	**Risk estimate adjustment**	**Risk of Bias**
risk estimate (e.g., odds ratio, hazard ratio)	1. Verified from medical record 2. Self-reported or not described	A. >1 factor adjusted B. ≤1 factor adjusted	1A = low 1B = moderate 2A = moderate 2B = high

Supplemental Table 4: Description of studies included in current meta-analysis

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
Ambroziak_2018[66]	Poland	MI: 158; 26y–49y No MI: 155; 30y–49y	M; F	DM (type 1 or type 2)	Medical history and treatment, or, fasting plasma glucose ≥126 mg/dL, or, glucose ≥200 mg/dL in oral glucose tolerance test.
				Family history of cardiac disease	MI or stroke in first degree relatives (men <55 years; women <65 years).
				Hypertension	Medical history and treatment, or, based on mean value of two measurements of sBP and dBP performed after at least 5 minutes sitting, made in 5-minute intervals. Hypertension defined as sBP ≥140 mmHg and/or dBP ≥90 mmHg.
				Smoking, current	Current smoker.
Antioniades_2005[67]	Greece	MI: 228; ≤49y No MI: 519; ≤49y	M; F	DM (type 1 or type 2)	---
				Dyslipidemia, not specified	Hypercholesterolemia, not described.
				Hypertension	---
				Smoking, prior	---
				Smoking, current	---
Arthes_1976[68]	USA	MI: 131; 30y–44y No MI: 1172; 30y–44y	F	DM (type 1 or type 2)	Clinical diagnosis, not described.
		MI: 136; 30y–44y No MI: 1391; 30y–44y		Race (White versus other)	Self-reported.
Bahrami_2015[69]	Iran	MI: 211; ≤50y No MI: 203; ≤50y	M; F	Dyslipidemia, not specified	Hyperlipidemia not described.
				Family history of cardiac disease	---
				Hypertension	---
				Smoking, current	---
Balogh_2018[70]	Hungary	MI: 119; ≤40y No MI: 101; ≤40y	M; F	DM (type 1 or type 2)	HbA1c ≥6.5 % (measured if diabetes was clinically suspected due to higher blood glucose values during hospitalization) or if diabetes was recorded in previous medical history.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
				Dyslipidemia	LDL cholesterol >3.4 mmol/L or on cholesterol-lowering medication.
				Family history of cardiac disease	Major cardiovascular event such as MI, stroke, or non-traumatic lower limb amputation in first-degree relative <60 years.
				Hypertension	sBP ≥140 mmHg and/or dBP ≥90 mmHg or on medication.
				Smoking, prior	Quit smoking ≥6 months prior to blood draw.
				Smoking, current	≥10 cigarettes/day for ≥6 months.
Benze_2002[71]	Germany	MI: 287 35y–45y No MI: 138 age-matched	M	DM (type 1 or type 2)	---
				Family history of cardiac disease	---
				Smoking, current	---
Caimi_2018[72]	Italy	MI: 120 19y–45y No MI: 50 19y–46y	M; F	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI 25-30 kg/m^2.
				BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
Celik_2008[73]	Turkey	MI: 129; 24y–45y No MI: 107; <45y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
				DM (type 1 or type 2)	Fasting glucose >126 mg/dL, non-fasting glucose >200 mg/dL and current use of medication.
				Total cholesterol >200 mg/dL	Fasting total cholesterol. Cut-off not reported.
				HDL cholesterol <60 mg/dL	Fasting HDL cholesterol. Used risk estimate for HDL cholesterol 28-63 mg/dL category.
				LDL cholesterol, high, not specified	Fasting LDL cholesterol; cut-off not reported.
				Triglycerides >150 mg/dL	Fasting triglyceride; cut-off not reported.
				Family history of cardiac disease	At least one first degree relative (men <55 years; women <65 years) with CAD.
				Hypertension	Seated sBP ≥140 mmHg, dBP ≥90 mmHg, or use of medication for hypertension within prior 2 weeks.
				Sex, male	Male versus female.
				Smoking, current	Current, regular smoker.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
Cetin_2017[74]	Turkey	MI: 168; <45y males; <55y females No MI: 224; <45y males; <55y females	M; F	DM (type 1 or type 2)	Fasting glucose >126 mg/dL and on medication.
				Dyslipidemia, not specified	Total cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL, triglyceride >150 mg/dL or on lipid-lowering medication.
				Family history of cardiac disease	CAD in parent or sibling (men <55 years; women <65 years).
				Hypertension	sBP >140 mmHg and/or dBP >90 mmHg, or on medication.
				Smoking, current	Current or quit smoking within 1 year prior to MI.
Choi_2018[75]	South Korea	MI: 5263 <52y (M 4932; F 331) No MI: 7257000 (M 1278907; F 5968793)	M;F	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI 25 – 29.9 kg/m^2 compared to normal BMI (18.5 – 22.9 kg/m^2)
				BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2 compared to normal BMI (18.5 – 22.9 kg/m^2)
Ciruzzi_1997[76]	Argentina	MI: 371; <55y No MI: 378; <55y	M; F	Family history of cardiac disease	Two or more family members (parents and siblings) with acute MI.
Danesh_1999[77]	UK	MI: 1122; 30y–49y No MI: 1122; 30y–49y	M; F	DM (type 1 or type 2)	Treated diabetes.
				Hypertension	Treated hypertension.
				Smoking, current	---
De Caterina_2011[78]	Italy, UK, USA	MI: 1864; <45y No MI: 1864; <45y	M; F	Triglycerides >150 mg/dL	Fasting triglyceride >150 mg/dL.
				Family history of cardiac disease	At least one parent, offspring, or sibling (men <55 years; women <65 years) with CAD.
				Smoking, current	Current smokers (regularly smoked during the three years preceding MI); former smokers (smoked regularly for ≥3 years but not during the year preceding the infarction); never smokers (never smoked regularly or had smoked regularly for <3 years).

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
				Alcohol, current	Moderate consumption (10–30 g ethanol /day); high consumption >30 g ethanol/day).
Doggen_2006[79]	The Netherlands	MI: 154; <50y No MI: 160; <50y	M	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
				BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI 25-30 kg/m^2.
				DM (type 1 or type 2)	MI: DM diagnosed from hospital discharge letters. No MI: DM diagnosed through interviews.
				Dyslipidemia	Medication for hypercholesterolemia.
				Hypertension	Medication for hypertension.
				Smoking, prior	Ex-smoker.
				Alcohol, current	Regular use.
Dogra_2012[80]	India	MI: 184; ≤40y No MI: 350; ≤40y	M; F	BMI ≥25 kg/m^2 versus <25 kg/m^2	High BMI (>23 kg/m^2) versus normal BMI (18.5–22.9 kg/m^2).
				DM (type 1 or type 2)	Fasting glucose >140 mg/dL or on medication.
				Family history of cardiac disease	At least one first or second degree relative with CAD.
				Hypertension	BP >140/90 mmHg or on medication.
				Smoking, current	Smoked ≥1g /day or smoked this amount for 1–3 months prior to interview.
				Alcohol, current	Current use.
Elmfeldt_1976[81]	Sweden	MI: 190 <55y No MI: 3035 <55y	M	Hypertension	Self-reported.
		MI: 190 <55y No MI: 2989 <55y		Smoking, current	Smoked ≥1 g/day or had smoked this amount for at least a month up to a time less than 3 months prior to the interview.
Emanuele_2010[82]	Italy	MI: 218; 24y–39y No MI: 258; 22y–39y	M; F	Smoking, current	---
Franco_2000[83]	Brazil	MI: 150; 25y–55y No MI: 150; 22y–55y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥27.3 kg/m^2 (women); BMI ≥30 kg/m^2 (men).
				DM (type 1 or type 2)	Diagnosis of DM or on medication.
				Dyslipidemia, not specified	Diagnosis of dyslipidemia or on medication.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
				Family history of cardiac disease	---
				Hypertension	Diagnosis of hypertension or on medication.
				Smoking, current	Recent history of regular cigarette consumption.
Friedlander_2001[84]	USA	MI: 107; 18y–44y No MI: 525; 18y–44y	F	DM (type 1 or type 2)	Self-report of physician-diagnosed DM.
				Family history of cardiac disease	MI in first-degree relative.
				Race	White versus other.
Gertler_1951[85]	USA	MI: 100; <40y No MI: 146;	M; F	Total cholesterol >200 mg/dL	Total cholesterol >305 mg/dL.
				Family history of cardiac disease	At least one parent with CHD.
Guella_2011[86]	Italy	MI: 1880; <45y No MI: 1880; <45y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI >30 kg/m^2.
				BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI 25-30 kg/m^2.
				DM (type 1 or type 2)	Self-report of physician-diagnosed DM.
				Dyslipidemia, not specified	Cholesterol >5.2 mmol/L or on statin therapy.
				Hypertension	sBP >140 mmHg and/or dBP >90 mmHg or on medication.
Gupta_2018[87]	India	MI: 125; ≤35y No MI: 103; ≤35y	M; F	Family history of cardiac disease	---
				Hypertension	---
				Smoking, current	---
				DM (type 1 or type 2)	---
				BMI ≥25 kg/m^2 versus <25 kg/m^2	---
Hamsten_1986A[88]	Sweden	MI: 116; <45y No MI: 116; <45y	M	DM (type 1 or type 2)	Fasting glucose ≥7.0 mmol/L.
				Hypertension	Medication for hypertension prior to MI or immediately post-MI or if sBP >160 mmHg and/or dBP >95 mmHg.
				Smoking, prior	Former smoker.
				Smoking, current	Current smoker; at least 1 cigarette or equivalent amount of tobacco each day.
Hbejan_2011[89]	Syria	MI: 287; 18y–45y No MI: 292; 18y–45y	M	DM (type 1 or type 2)	Self-reported.
				Dyslipidemia, not specified	Self-reported.
				Family history of cardiac disease	At least one first-degree relative with MI.
				Hypertension	Self-reported.
		MI: 329;	M; F	Smoking, prior	Quit smoking >6 months prior to MI.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
		18y–45y No MI: 778 18y–45y		Smoking, current	Quit smoking <6 months prior to MI.
Iacoviello_2005[90]	Italy	MI: 374; <45y males; <50y females No MI: 386; <45y males; <50y females	M; F	DM (type 1 or type 2)	Fasting glucose ≥140 mg/dL or on medication.
		MI: 382; <45y males; <50y females No MI: 402; <45y males; <50y females		Dyslipidemia, not specified	Hypercholesterolemia (≥200 mg/dL), hypertriglyceridemia (≥200 mg/dL), HDL cholesterol (≤35 mg/dL), or on lipid-lowering medication.
		MI: 313; <45y males; <50y females No MI: 312; <45y males; <50y females		Family history of cardiac disease	≥1 first-degree relative (<60 years) with MI.
		MI: 368; <45y males; <50y females No MI: 384; <45y males; <50y females		Hypertension	BP ≥140/90 mmHg or on medication.
		MI: 378; <45y males; <50y females No MI: 395; <45y males; <50y females		Smoking, prior	Former smoker.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
		MI: 378; <45y males; <50y females No MI: 395; <45y males; <50y females		Smoking, current	Current smoker.
Inbal_1999[91]	Israel	MI:109; 29y–52y No MI: 187; 26y–52y	M	DM (type 1 or type 2)	From medical chart, not described.
		MI: 106; 29y–52y No MI: 177; 26y–52y		Total cholesterol >200 mg/dL	Serum cholesterol level >200 mg/dL on hospital admission.
		MI: 111; 29y–52y No MI: 184; 26y–52y		Hypertension	sBP ≥140 mmHg on hospital admission.
		MI: 112; 29y–52y No MI: 187; 26y–52y		Smoking, prior	Former smoker.
		MI: 112; 29y–52y No MI: 187; 26y–52y		Smoking, current	Current smoker.
Jolly_2010[92]	USA	MI: 7261; 35–54y	M; F	Race	Black versus other.
Kaufman_1983[93]	USA	MI: 502; 30y–54y No MI: 835; 30y–54y	M	Smoking, prior	Ex-smoker versus never.
				Smoking, current	Any number of cigarettes/day.
Kaufman_1985[94]	USA	MI: 2170;	M	Alcohol, current	Any alcohol intake.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
		30y–54y No MI: 981; 30y–54y		Alcohol, prior	Last drink ≥1 year prior to admission.
Khare_2005[95]	India	MI: 120; <40y No MI: 40; <40y	M; F	Family history of cardiac disease	---
Kinjo_2002[96]	Japan	MI: 121; <55y No MI: 182; <55y	M; F	DM (type 1 or type 2)	Fasting plasma glucose ≥126 mg/dL or on medication.
				Hypertension	BP ≥140/90 mmHg or on medication.
				Smoking, current	Current or prior smoking.
La Vecchia_1987A[97]	Italy	MI: 168; <55y No MI: 1122; 23y–54y	F	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI ≥25 versus <25 kg/m^2.
La Vecchia_1987B[98]	Italy	MI: 202; <55y No MI: 374; 23y–54y	F	DM (type 1 or type 2)	Self-reported.
				Dyslipidemia, not specified	Self-reported.
				Family history of cardiac disease	Self-reported.
				Hypertension	Self-reported.
				Smoking, prior	Self-reported.
				Smoking, current	Self-reported.
Le Cam-Duchez _2009[99]	France	MI: 176; <46y No MI: 176; <46y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI >30 kg/m^2.
				Dyslipidemia, not specified	---
				Family history of cardiac disease	---
				Smoking, current	---
Lee_2020[34]	South Korea	Age 20–39y at enrollment; follow-up within 8 years	M; F	Total cholesterol	Top vs. lowest quartile
				HDL cholesterol	Top vs. lowest quartile
				LDL cholesterol	Top vs. lowest quartile
				Triglycerides	Top vs. lowest quartile
Leitersdorf_1986[100]	Israel	MI: 258; <55y No MI: 377; <55y	M	DM (type 1 or type 2)	MI: self-reported physician diagnosis. No MI: 12 hour fasting glucose ≥120 mg/dL.
				Hypertension	MI: self-reported physician diagnosis. No MI: BP ≥150/100 mmHg or on medication.
				Smoking, prior	Quit smoking ≥1 month prior to interview.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
				Smoking, current	Smoked ≥1 cigarette/day for up to 1 month before interview.
Li_2017[101]	China	MI: 267; ≤44y No MI: 247; ≤44y	M	DM (type 1 or type 2)	Fasting glucose ≥7.0 mmol/L, 2-hour postprandial glucose >11.1 mmol/L, or on medication.
				Family history of cardiac disease	CHD in first degree relative (men <55 years; women <65 years).
				Hypertension	BP ≥140/90 mmHg and/or on medication.
				Smoking, current	Smoking within 1 month of hospital admission.
				Alcohol, current	Not reported.
Lima-Neto_2013[102]	Brazil	MI: 102; <45y No MI: 108; <45y	M; F	Alcohol, current	Daily intake ≥1 g beer, wine, or distilled spirits.
Liu_2007[103]	Taiwan	MI: 200; <45y No MI: 200; <45y	M; F	DM (type 1 or type 2)	Fasting glucose >126 mg/dL or on medication.
				Family history of cardiac disease	Premature-onset MI or sudden cardiac death among first-degree relatives.
				Hypertension	BP >140/90 mmHg on three occasions or on medication.
				Smoking, current	Current smoker.
Maddhuri_2018[104]	India	MI: 300; 20y–40y No MI: 300; 20y–40y	M; F	Family history of cardiac disease	Family history of CAD.
				Smoking, current	---
				Alcohol, current	---
Maino_2016[105]	The Netherlands	MI: 218; 18y–50y No MI: 743; 18y–50y	F	Alcohol, current	---
Malinauskiene_2010[106]	Lithuania	MI: 122; 35y–61y No MI: 371; 35y–61y	F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
				Hypertension	BP ≥140/90 mmHg.
				Smoking, current	Current smoker.
Medina_2008[107]	Spain	MI: 689; <51y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
				DM (type 1 or type 2)	Prior diagnosis, fasting glucose >126 mg/dL, or medication for DM.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
		No MI: 697; <51y		Dyslipidemia, not specified	Prior diagnosis, total cholesterol >250 mg/dL and/or triglycerides >175 mg/dL.
				Hypertension	Prior diagnosis, BP ≥140/90 mmHg on ≥2 separate occasions, or on medication.
				Smoking, current	Current/prior smoking in previous 10 years.
Montes_2005[32]	Italy	MI: 165; <45y No MI: 165; age matched (±3y)	F	HDL/total cholesterol ratio	Risk of MI per 0.1 unit drop in ratio.
Negri_1995[108]	Italy	MI: 542; <50y No MI: 705; <50y	M; F	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI ≥ 25 versus <25.
				Diabetes (type 1 or type 2)	Self-reported.
				Total cholesterol >200 mg/dL	≥226 mg/dL versus <188 mg/dL. Measured during hospitalization.
				Fam history of cardiac disease	At least 1 first-degree relative with AMI before age 65 years.
				Hypertension	Self-reported.
				Smoking, current	≥20 cigarettes/day.
Nora_1980[109]	USA	MI: 207; 35y–54y No MI: 621; 35y–54y	M; F	Total cholesterol >200 mg/dL	Total cholesterol >220 mg/dL.
				Triglycerides >150 mg/dL	Triglycerides >200 mg/dL.
				Family history of cardiac disease	First degree relative <65 years with ischemic heart disease.
				Hypertension	BP ≥140/90 mmHg.
				Smoking, current	Smoking > half-pack per day.
Oliveira_2009A[110]	Portugal	MI: 257; ≤45y No MI: 256; ≤45y	M	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
				BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI 25-29.9 kg/m^2.
Oliveira_2009B[30]	Portugal	MI: 270; ≤45y No MI: 289; ≤45y	M	Obesity, waist-to-hip ratio	Ratio >0.90 versus ≤0.90.
				DM (type 1 or type 2)	Self-reported.
				Dyslipidemia, not specified	Self-reported.
				Family history of cardiac disease	At least one first degree relative with MI or sudden death.
				Hypertension	Self-reported.
				Smoking, current	Current smoker.
				Alcohol, current	Any alcohol intake.
				Alcohol, never	Never versus 0.1–30.0 g/day.
Palacin_2011[111]	Spain	MI: 500; <55y No MI: 500;	M	DM (type 1 or type 2)	Prior diagnosis, fasting glucose >15 mmol/L on >2 occasions, or on medication.
				Dyslipidemia, not specified	Prior diagnosis, fasting total cholesterol >250 mg/dL, or lipid-lowering medication.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
		<55y		Hypertension	Prior diagnosis, sBP >140 mmHg and/or dBP >90 mmHg, or on medication.
				Smoking, current	Current smoker.
Panagiotakos_2008[112]	Greece	MI: 100; <36y No MI: 100; <36y	M; F	Family history of cardiac disease	Premature CHD in first-degree relatives (men <55 years; women <65 years) including MI, sudden death, coronary arteries bypass grafting procedure or percutaneous coronary angioplasty.
Qian_2015[31]	China	MI: 341; ≤40y No MI: 341; ≤40y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	Obesity, not described.
				DM (type 1 or type 2)	Per American Diabetes Association guidelines.
				Dyslipidemia, not specified	Per National Cholesterol Education Program Adult Treatment Panel III Guidelines.
				Family history of cardiac disease	---
				Hypertension	Per 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
				Smoking, current	Smoked regularly for ≥6 months.
Rallidis_2017A[113]	Greece	MI: 327; ≤35y No MI: 167; ≤35y	M; F	DM (type 1 or type 2)	Fasting glucose >125 mg/dL or on medication.
				Hypertension	BP ≥140/90 mmHg or on medication.
				Smoking, current	Current smoker.
Rallidis_2017B[114]	Greece	MI: 255; ≤35y No MI: 400; ≤35y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
				Dyslipidemia, not specified	Total cholesterol >200 mg/dL or cholesterol lowering medication.
Reiner_2007[115]	USA	MI: 264; 23y–59y No MI: 407; 18y–59y	F	Dyslipidemia, not specified	Self-reported.
				Hypertension	Self-reported.
				Smoking, current	Current smoker.
Rivera-Garcia_2013[116]	Mexico	MI: 275; ≤45y No MI: 278; ≤45y	M; F	DM (type 1 or type 2)	Prior diagnosis or fasting glucose >126 mg/dL.
				Dyslipidemia, not specified	Cholesterol level of 200 mg/dL or lipid-lowering medication.
				Family history of cardiac disease	CAD or sudden death in a first degree relative (men <55 years; women <65 years).

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
				Hypertension	Per European Society Cardiology criteria or on medication.
				Smoking, current	Current or quit within 12 months prior to MI.
Roldan_2005[117]	Spain	MI: 281; <45y No MI: 550; <45y	M; F	DM (type 1 or type 2)	Not reported.
				Hypertension	sBP >140 mmHg and/or dBP >90 mmHg on repeat observations over 3 months or, if no blood pressure values were available when the participant was under treatment with medication for chronic hypertension.
				Sex	Males versus females.
				Smoking, current	>10 cigarettes/day.
Rosenberg_1980C[118]	USA	MI: 477; 30y–49y No MI: 1832; 30y–49y	F	DM (type 1 or type 2)	Information obtained from patient using standard questionnaire for medical and surgical history.
				Hypertension	Information obtained from patient using standard questionnaire for medical and surgical history.
				Race	White versus other
Rosenberg_1981[119]	USA	MI: 511; 30y–49y No MI: 899; 30y–49y	F	Alcohol, current	Alcohol <12 months prior to admission versus never.
				Alcohol, prior	Alcohol ≥12 months prior to admission) versus never.
Rosenberg_1983[120]	USA	MI: 249; 25y–49y No MI: 686; 25y–49y	F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥35 kg/m^2 versus 21–27 kg/m^2.
		MI: 254; 25y–49y No MI:798; 25y–49y		Total cholesterol >200 mg/dL	Total cholesterol >200 mg/dL.
		MI: 254; 25y–49y No MI: 793; 25y–49y		HDL cholesterol <60 mg/dL	HDL cholesterol <60 mg/dL.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
		MI: 255; 25y–49y No MI: 802; 25y–49y		Family history of cardiac disease	MI or stroke in first-degree relative <60 years.
Rosenberg_1985[121]	USA	MI: 554; <50y No MI: 1840; <50y	F	Smoking, prior	Ex-smoker versus never.
				Smoking, current	Current smoker.
Russo_2012[122]	Italy	MI: 174; 18y–40y No MI: 142; age (±1y) matched	M; F	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI >25 kg/m^2.
		MI: 196; 18y–40y No MI: 164; age (±1y) matched		DM (type 1 or type 2)	Medical history, fasting glucose >126 mg/dL on two occasions or glucose overload test.
		MI: 191; 18y–40y No MI: 160; age (±1y) matched		Total cholesterol >200 mg/dL	Total cholesterol >220 mg/dL.
		MI: 196; 18y–40y No MI: 85; age (±1y) matched		Family history of cardiac disease	Family history of CHD or atherosclerotic vascular disease in men <55 years or women <65 years.
		MI: 196; 18y–40y No MI: 164; age (±1y) matched		Hypertension	BP ≥140/90 mmHg or on medication.
		MI: 189; 18y–40y No MI: 164; age (±1y) matched		Smoking, current	Current smokers.
Saigo_2001[123]	Japan	MI: 140; <45y	M	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI ≥25 kg/m^2.
				DM (type 1 or type 2)	Glucose ≥127 mg/dL and/or medication.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
		No MI: 150; <45y		Dyslipidemia, not specified	Total cholesterol ≥220 mg/dL or triglycerides ≥150 mg/dL and/or lipid-lowering medication.
				Hypertension	sBP ≥140 mmHg and/or dBP ≥95 mmHg or on medication.
				Smoking, current	Not reported.
Sala_2001[124]	Italy	MI: 125; <45y No MI: 108; <45y	M	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI >27 kg/m^2 versus ≤27 kg/m^2
Sampaio_2007[125]	Brazil	MI: 121; <40y No MI: 111; <40y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI ≥30 kg/m^2.
				DM (type 1 or type 2)	Fasting glucose >126 mg/dL or on medication.
				LDL cholesterol, high, not specified	High LDL cholesterol, but not described.
				Family history of cardiac disease	First degree relative (men <55 years; women <65 years) with MI.
				Hypertension	BP >140/90 mmHg or on medication.
				Race	White versus other.
				Smoking, current	Smokes ≥3 cigarettes/day.
Sandkamp_1990[126]	Germany	MI: 509; <46y No MI: 1053; <46y	M	BMI ≥30 kg/m^2 versus <30 kg/m^2	BMI >30 kg/m^2.
Sastry_2006[127]	UK	MI: 101; 19y–39y No MI: 101; 19y–39y	M; F	BMI ≥25 kg/m^2 versus <25 kg/m^2	Elevated BMI, cut-off not reported.
				DM (type 1 or type 2)	---
				Dyslipidemia, not specified	Total cholesterol, but not described.
				Hypertension	---
				Smoking	---
Schargrodsky_1994[128]	Argentina	MI: 127; 30y–65y No MI: 127; 30y–65y	F	DM (type 1 or type 2)	Self-reported history.
				Family history of cardiac disease	Self-reported family history of CHD.
				Hypertension	Self-reported diagnosis.
				Smoking, prior	Ex-smoker.
				Smoking, current	Current smoker.
Siegerink_2012[129]	The Netherlands	MI: 248; 18y-50y No MI: 925; 18y–50y	F	DM (type 1 or type 2)	Self-reported diagnosis or on medication.
				Dyslipidemia, not specified	Self-reported hypercholesterolemia or on medication.
				Family history of cardiac disease	MI <60 years in first degree relative.
				Hypertension	Self-reported diagnosis or on medication.
				Race	White versus other.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
				Smoking, current	Smoking in the year prior to MI.
Singh_2010[130]	India	MI: 108; <55 males; <65 females No MI: 108; <55 males; <65 females	M; F	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI ≥25 kg/m^2.
				DM (type 1 or type 2)	---
				Hypertension	---
				Smoking, current	---
Sniderman_2016[33]	see Yusuf_2004	MI: 2347; 18y–50y No MI: 3438; 18y–50y	M; F	Total cholesterol, per SD change	Laboratory measurement of total cholesterol.
				HDL cholesterol, per SD change	Laboratory measurement of HDL cholesterol.
				LDL cholesterol, per SD change	Laboratory measurement of LDL cholesterol.
				Non-HDL cholesterol, per SD change	Calculated from total and HDL cholesterol.
				Apo A1, per SD change	Laboratory measurement of Apo A1.
				Apo B, per SD change	Laboratory measurement of Apo B.
Tanis_2006[131]	The Netherlands	MI: 200; 18y–49y No MI: 626; 18y–49y	F	BMI ≥25 kg/m^2 versus <25 kg/m^2	BMI ≥27.3 kg/m^2.
				C-reactive protein	0.50–1.34 mg/L.
					1.34–4.97 mg/L.
					≥4.97 mg/L.
Vaccarino_2018[132]	USA	MI: 150; ≤61y No MI: 58; ≤61y	F	Race	Black versus other.
Walker_1967[133]	USA	MI: 100; <40y No MI: 72; <40y	M	Family history of cardiac disease	Self-reported.
				Hypertension	Self-reported.
				Race	Black versus other.
				Smoking, current	>1 pack/day.
				Alcohol, current	>2 oz. whiskey/day.
Westover_2008[134]	USA	MI: 11011; 18y–44y No MI: 3137154; 18y–44y	M; F	BMI ≥30 kg/m^2 versus <30 kg/m^2	ICD code for obesity.
				DM (type 1 or type 2)	ICD code for diabetes.
				Dyslipidemia, not specified	ICD code for lipid disorders.
				Hypertension, current	ICD code for hypertension.
				Smoking, current	ICD code for smoking.
				Alcohol, current	ICD code for alcohol abuse.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
Yamac_2018[135]	Turkey	MI: 108; <45y No MI: 91; <45y	M; F	Family history of cardiac disease	Not reported.
Yusuf_2004[20]	Argentina, Australia, Bahrain, Bangladesh, Benin, Botswana,	MI: 12461; ≤55y males; ≤65 females No MI: 14637; age (±5y) matched	M; F	Obesity, waist-to-hip ratio	Waist-to-hip ratio.
				DM (type 1 or type 2)	Self-reported.
				ApoB/ApoA1	Top versus lowest quartile.
				Hypertension	Self-reported.
				Smoking, current	Smoked any tobacco in prior 12 months and those who quit within prior year.

Study	Countries	Number of participants; age	Sex	Risk factor for current meta-analysis	Risk factor definition provided by study authors
	Brazil, Cameroon, Canada, Chile, China, Colombia, Croatia, Czech Republic, Egypt, Germany, Greece, Guatemala, Hong Kong, Hungary, India, Italy, Iran, Israel, Japan, Kenya, Kuwait, Malaysia, Mexico, Mozambique, Nepal, New Zealand, Nigeria, Oman, Pakistan, Philippines, Poland, Portugal, Qatar, Russia, Seychelles, Singapore, Spain, South Africa, Sri Lanka, Sweden, Thailand, The Netherlands, UAE, UK, USA, Zimbabwe			Alcohol, current	Use ≥3 times/week.
Zoller_2015[136]	Sweden	MI: 329; 18y–38y No MI: 1970630; 18y–38y	M; F	DM (type 1 or type 2)	ICD code for diabetes.
				Family history of cardiac disease	ICD code for family history.
				Hypertension	ICD code for hypertension.
				Sex	Males versus females.

Abbreviations: apo: apolipoprotein; BMI: body-mass index; BP: blood pressure; CAD: coronary artery disease; CHD: coronary heart disease; dBP: diastolic blood pressure; DM: diabetes mellitus; F: female; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; ICD: international classification of diseases; LDL: low-density lipoprotein; M: male; MI: myocardial infarction; sBP: systolic blood pressure; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America; WHO: World Health Organization

Supplemental Table 5: Number of participants per risk factor, categorized by risk of bias

Risk factor	no. studies (no. participants)	Risk of bias					
		Low		Medium		High	
		no. studies (%)	no. participants (%)	no. studies (%)	no. participants (%)	no. studies (%)	no. participants (%)
Demographics							
Sex (males versus females)	3 (n=1972026)	3 (100)	1972026 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Race (White versus other)	5 (n=5874)	0 (0)	0 (0)	5 (100)	5874 (100)	0 (0)	0 (0)
Race (Black versus other)	3 (n=7641)	0 (0)	0 (0)	2 (67)	380 (5)	1 (33)	7261 (95)
Family history of cardiac disease	35 (n=1990987)	0 (0)	0 (0)	10 (29)	1977134 (99.3)	25 (71)	13853 (0.7)
Lifestyle risk factors							
Smoking, current	48 (n=3209848)	0 (0)	0 (0)	11 (23)	3181092 (99.1)	37 (77)	28756 (0.9)
Smoking, prior	12 (n=8879)	0 (0)	0 (0)	2 (17)	2435 (27.4)	10 (83)	6444 (72.6)
Alcohol, current	13 (n=3187345)	0 (0)	0 (0)	4 (31)	3177207 (99.7)	9 (69)	10138 (0.3)
Alcohol, prior	2 (n=4561)	0 (0)	0 (0)	2 (100)	4561	0 (0)	0 (0)
Alcohol, never	1 (n=559)	0 (0)	0 (0)	1 (100)	559	0 (0)	0 (0)
Clinical risk factors							
Diabetes (type 1 or type 2)	42 (n=5174321)	4 (10)	2610 (0.1)	22 (52)	5160352 (99.7)	16 (38)	11131 (0.2)
Hypertension	45 (n=5177526)	7 (16)	7159 (0.1)	22 (49)	5156422 (99.6)	16 (36)	13945 (0.3)
Dyslipidemia, not specified	21 (n=3163027)	4 (19)	5989 (0.2)	9 (43)	3152809 (99.7)	8 (38)	4229 (0.1)
BMI ≥30 versus <30 kg/m^2	16 (n=4382036)	5 (31)	1225351 (28)	10 (63)	3156003 (72)	1 (6)	682 (0.02)
BMI ≥25 versus <25 kg/m^2	15 (n=1821224)	7 (47)	1815192 (99.7)	6 (40)	5602 (0.3)	2 (13)	430 (.02)
Biomarkers							
Total cholesterol >200 versus ≤200 mg/dL	8 (n=5129)	1 (13)	1386 (27)	6 (75)	2996 (58)	1 (13)	747 (15)
Total cholesterol, per SD increment	1 (n=5785)	1 (100)	5785 (100)	0 (0)	0 (0)	0 (0)	0 (0)
LDL cholesterol, high, not specified	2 (n=468)	0 (0)	0 (0)	1 (50)	236 (50.4)	1 (50)	232 (49.6)
Triglycerides >150 versus ≤150 mg/dL	3 (n=1064)	1 (33)	236 (22)	2 (67)	828 (78)	0 (0)	0 (0)
HDL cholesterol <60 versus ≥60 mg/dL	2 (n=1283)	0 (0)	0 (0)	2 (100)	1283 (100)	0 (0)	0 (0)
HDL/total cholesterol ratio, per 0.1 drop	1 (n=1386)	1 (100)	1386 (100)	0 (0)	0 (0)	0 (0)	0 (0)
LDL cholesterol, per SD increment	1 (n=5785)	1 (100)	5785 (100)	0 (0)	0 (0)	0 (0)	0 (0)
HDL cholesterol, per SD increment	1 (n=5785)	1 (100)	5785 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Non-HDL cholesterol, per SD increment	1 (n=5785)	1 (100)	5785 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Apo A1, per SD increment	1 (n=5785)	1 (100)	5785 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Apo B, per SD increment	1 (n=5785)	1 (100)	5785 (100)	0 (0)	0 (0)	0 (0)	0 (0)
ApoB/ApoA1, top vs. lowest quintile	1 (n=27098)	1 (100)	27098 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Total cholesterol, top vs. lowest tertile	1 (n=5688055)	0 (0)	0 (0)	1 (100)	5688055 (100)	0 (0)	0 (0)
HDL cholesterol, top vs. lowest tertile	1 (n=5688055)	0 (0)	0 (0)	1 (100)	5688055 (100)	0 (0)	0 (0)
LDL cholesterol, top vs. lowest tertile	1 (n=5688055)	0 (0)	0 (0)	1 (100)	5688055 (100)	0 (0)	0 (0)
Triglycerides, top vs. lowest tertile	1 (n=5688055)	0 (0)	0 (0)	1 (100)	5688055 (100)	0 (0)	0 (0)

Estimated number of participants includes MI and MI-free groups. Percentages may not add up to 100 due to rounding. Risk of bias determined using criteria described in supplementary file 3.
Abbreviations: Apo: apolipoprotein; BMI: body-mass index; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SD: standard deviation.

Supplemental Table 6: Risk of bias of individual risk factors and adjusted covariates in multivariable models

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
Ambroziak_2018[66]	DM (type 1 or type 2)	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Smoking, current	---	high
Antioniades_2005[67]	DM (type 1 or type 2)	---	high
	Dyslipidemia, not specified	---	high
	Hypertension	---	high
	Smoking, prior	---	high
	Smoking, current	---	high
Arthes_1976[68]	DM (type 1 or type 2)	---	medium
	Race (White versus other)	---	medium
Bahrami_2015[69]	Dyslipidemia, not specified	---	high
	Family history of cardiac disease	---	high
	Hypertension	---	high
	Smoking, current	---	high
Balogh_2018[70]	DM (type 1 or type 2)	---	medium
	Dyslipidemia	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Smoking, prior	---	high
	Smoking, current	---	high
Benze_2002[71]	DM (type 1 or type 2)	---	high
	Family history of cardiac disease	---	high
	Smoking, current	---	high
Caimi_2018[72]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	medium
Celik_2008[73]	DM (type 1 or type 2)	---	medium
	BMI ≥30 kg/m^2 versus <30 kg/m^2	backward stepwise logistic regression models with sex, obesity, smoking, hypertension, family history, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) C677T mutation.	low
	Total cholesterol >200 mg/dL		medium
	HDL cholesterol <60 mg/dL		medium
	LDL cholesterol, high, not specified		medium
	Triglycerides >150 mg/dL		low
	Family history of cardiac disease		medium
	Hypertension		low
	Sex (males versus females)		low
	Smoking, current		medium
Cetin_2017[74]	DM (type 1 or type 2)	---	medium
	Dyslipidemia, not specified	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
	Smoking, current	---	high
Choi_2018[75]	BMI ≥30 kg/m^2 versus <30 kg/m^2	age, household income, physical activity, tobacco and alcohol consumption, systolic blood pressure, fasting serum glucose level, total cholesterol level, and Charlson comorbidity index.	low
	BMI ≥25 kg/m^2 versus <25 kg/m^2		low
Ciruzzi_1997[76]	Family history of cardiac disease	age, sex, cholesterolemia, smoking, DM, hypertension, BMI, education, social class, and physical exercise.	medium
Danesh_1999[77]	DM (type 1 or type 2)	---	high
	Hypertension	---	high
	Smoking, current	---	high
De Caterina_2011[78]	Triglycerides >150 mg/dL	---	medium
	Family history of cardiac disease	---	high
	Smoking, current	---	high
	Alcohol, current	---	high
Doggen_2006[79]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	medium
	DM (type 1 or type 2)	---	high
	Dyslipidemia	---	high
	Hypertension	---	medium
	Smoking, prior	---	high
	Alcohol, current	---	high
Dogra_2012[80]	BMI ≥25 kg/m^2 versus <25 kg/m^2	age, sex	low
	DM (type 1 or type 2)	age, sex	low
	Family history of cardiac disease	age, sex	medium
	Hypertension	age, sex	low
	Smoking, current	age, sex	medium
	Alcohol, current	age, sex	medium
Elmfeldt_1976[81]	Hypertension	---	high
	Smoking, current	---	high
Emanuele_2010[82]	Smoking, current	---	high
Franco_2000[83]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	DM (type 1 or type 2)	---	high
	Dyslipidemia, not specified	---	high
	Family history of cardiac disease	---	high
	Hypertension	---	high
	Smoking, current	---	high
Friedlander_2001[84]	DM (type 1 or type 2)	---	high
	Family history of cardiac disease	risk factors [not specified] and person-years at risk among first-degree relatives	medium
	Race (White versus other)	---	medium
Gertler_1951[85]	Total cholesterol >200 mg/dL	---	medium
	Family history of cardiac disease	---	high

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
Guella_2011[86]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	medium
	DM (type 1 or type 2)	cardiovascular risk factors	medium
	Dyslipidemia, not specified	cardiovascular risk factors	low
	Hypertension	cardiovascular risk factors	low
Gupta_2018[87]	Family history of cardiac disease	---	high
	Hypertension	---	high
	Smoking, current	---	high
	DM (type 1 or type 2)	---	high
	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	high
Hamsten_1986[88]	DM (type 1 or type 2)	---	medium
	Hypertension	---	medium
	Smoking, prior	---	high
	Smoking, current	---	high
Hbejan_2011[89]	DM (type 1 or type 2)	---	high
	Dyslipidemia, not specified	---	high
	Family history of cardiac disease	---	high
	Hypertension	---	high
	Smoking, prior	gender, age, family history of MI, BMI, total energy intake, alcohol and caffeine consumption, leisure-time physical activity, presence (yes or no) of angina, dyslipidemia, hypertension, and DM	medium
	Smoking, current	---	high
Iacoviello_2005[90]	DM (type 1 or type 2)	---	medium
	Dyslipidemia, not specified	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Smoking, prior	---	high
	Smoking, current	---	high
Inbal_1999[91]	DM (type 1 or type 2)	---	high
	Total cholesterol >200 mg/dL	---	medium
	Hypertension	---	medium
	Smoking, prior	---	high
	Smoking, current	---	high
Jolly_2010[92]	Race (Black versus other)	---	high
Kaufman_1983[93]	Smoking, prior	age, geographic region of interview, drug treatment for hypertension, history of elevated cholesterol, drug treatment for DM, family history of MI or stroke, personality score, alcohol consumption, religion, and marital status.	medium
	Smoking, current	---	high
Kaufman_1985[94]	Alcohol, current	---	high

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
	Alcohol, prior	age, geographic region of hospital, religion, marital status, years of education, cigarette smoking, history of drug treatment for hypertension, history of abnormal blood lipids, history of drug treatment for DM, BMI, family history of MI or stroke, personality score, and minutes of aerobic exercise per week.	medium
Khare_2005[95]	Family history of cardiac disease	---	high
Kinjo_2002[96]	DM (type 1 or type 2)	---	medium
	Hypertension	---	medium
	Smoking, current	---	high
La Vecchia_1987[97]	BMI ≥25 kg/m^2 versus <25 kg/m^2	geographic area, marital status, education, social class, cigarette smoking, alcohol and coffee consumption, parity, age at menopause, diabetes, hypertension, obesity, hyperlipidemia, family history of ischemic heart disease, and oral contraceptive and other female hormone use.	low
La Vecchia_1987[98]	DM (type 1 or type 2)	---	high
	Dyslipidemia, not specified	---	high
	Family history of cardiac disease	---	high
	Hypertension	---	high
	Smoking, prior	---	high
	Smoking, current	---	high
Le Cam-Duchez _2009[99]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	Dyslipidemia, not specified	Protein Z (vitamin K-dependent glycoprotein) polymorphisms	medium
	Family history of cardiac disease	Protein Z (vitamin K-dependent glycoprotein) polymorphisms	medium
	Smoking, current	Protein Z (vitamin K-dependent glycoprotein) polymorphisms	medium
Lee_2020[34]	Total cholesterol	---	medium
	HDL cholesterol	---	medium
	LDL cholesterol	---	medium
	Triglycerides	---	medium
Leitersdorf_1986[100]	DM (type 1 or type 2)	---	high
	Hypertension	---	high
	Smoking, prior	---	high
	Smoking, current	---	high
Li_2017[101]	DM (type 1 or type 2)	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Smoking, current	---	high
	Alcohol, current	---	high
Lima-Neto_2013[102]	Alcohol, current	---	high
Liu_2007[103]	Family history of cardiac disease	---	high
	DM (type 1 or type 2)	multiple logistic regression model with smoking, DM, hypertension, and CYP2J2*7 T allele	low
	Hypertension		low

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
	Smoking, current		medium
Maddhuri_2018[104]	Family history of cardiac disease	---	high
	Smoking, current	---	high
	Alcohol, current	---	high
Maino_2016[105]	Alcohol, current	---	high
Malinauskiene_2010[106]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	Hypertension	---	medium
	Smoking, current	---	high
Medina_2008[107]	BMI ≥30 kg/m^2 versus <30 kg/m^2	age, sex, smoking, dyslipidemia, hypertension, DM, BMI ≥30 kg/m^2, presence of endothelial protein C receptor (EPCR) alleles A3 (4600G allele) and A1 (4678C allele)	low
	DM (type 1 or type 2)		low
	Dyslipidemia, not specified		low
	Hypertension		low
	Smoking, current		medium
Montes_2005[32]	HDL/total cholesterol ratio	BMI, hypertension, family history of coronary heart disease, smoking, DM, menopause, estrogen use, triglycerides, antibodies to endothelial protein C receptor (IgA and IgM)	low
Negri_1995[108]	BMI ≥25 kg/m^2 versus <25 kg/m^2	sex, age, area of residence, education, smoking, cholesterol (mg/dL) tertiles (<188; 188-225; ≥226), hypertension, DM, BMI, family history of acute MI	low
	Diabetes (type 1 or type 2)		medium
	Total cholesterol >200 mg/dL		low
	Fam history of cardiac disease		medium
	Hypertension		medium
	Smoking, current		medium
Nora_1980[109]	Total cholesterol >200 mg/dL	---	medium
	Triglycerides >150 mg/dL	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Smoking, current	---	high
Oliveira_2009[110]	BMI ≥30 kg/m^2 versus <30 kg/m^2	age, education, smoking and family history of acute MI	low
	BMI ≥25 kg/m^2 versus <25 kg/m^2		low
Oliveira_2009[30]	Obesity, waist-to-hip ratio	age, education, family history of MI, waist-to-hip ratio, smoking, total energy intake and leisure-time physical activity. Also adjustments for hypertension, dyslipidemia and diabetes were made for all variables, except for waist-to-hip ratio	low
	DM (type 1 or type 2)		medium
	Dyslipidemia, not specified		medium
	Family history of cardiac disease		medium
	Hypertension		medium
	Alcohol, never		medium
	Smoking, current	---	high
	Alcohol, current	---	high
Palacin_2011[111]	DM (type 1 or type 2)	---	medium
	Dyslipidemia, not specified	---	medium
	Hypertension	---	medium
	Smoking, current	---	high
Panagiotakos_2008[112]	Family history of cardiac disease	---	high

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
Qian_2015[31]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	high
	DM (type 1 or type 2)	---	medium
	Dyslipidemia, not specified	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Smoking, current	---	high
Rallidis_2017A[113]	DM (type 1 or type 2)	---	medium
	Hypertension	---	medium
	Smoking, current	---	high
Rallidis_2017B[114]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	Dyslipidemia, not specified	---	medium
Reiner_2007[115]	Dyslipidemia, not specified	---	high
	Hypertension	---	high
	Smoking, current	---	high
Rivera-Garcia_2013[116]	DM (type 1 or type 2)	platelet glycoprotein IIIA PIA1/A2 polymorphisms and traditional cardiovascular risk factors	medium
	Dyslipidemia, not specified		low
	Family history of cardiac disease		medium
	Hypertension		low
	Smoking, current		medium
Roldan_2005[117]	DM (type 1 or type 2)	sex, smoking, hypertension, DM, hypercholesterolemia, C46T factor XII polymorphism	medium
	Hypertension		medium
	Sex (males versus females)		low
	Smoking, current		medium
Rosenberg_1980C[118]	DM (type 1 or type 2)	---	high
	Hypertension	---	high
	Race (White versus other)	---	medium
Rosenberg_1981[119]	Alcohol, current	age, location of hospital, religion, years of education, menopausal status, number of visits to a physician or clinic in preceding year, cigarette smoking, hypertension, DM, history of abnormal blood lipids, history of obesity, year of admission, and oral contraceptive use within preceding year.	medium
	Alcohol, prior		medium
Rosenberg_1983[120]	BMI ≥30 kg/m^2 versus <30 kg/m^2	age, geographic region of admitting hospital, oral contraceptive use, and other factors evaluated in the study	low
	Total cholesterol >200 mg/dL	---	medium
	HDL cholesterol <60 mg/dL	---	medium
	Family history of cardiac disease	---	high
Rosenberg_1985[121]	Smoking, prior	age, geographic area, oral contraceptive use, total serum cholesterol, HDL cholesterol, history of drug treated hypertension, history of drug treated angina pectoris, history of drug-treated DM, menopausal status, BMI, blood group, family history of MI or stroke in a parent or sibling before age 60 years, and personality score	high

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
	Smoking, current	---	high
Russo_2012[122]	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	medium
	DM (type 1 or type 2)	---	medium
	Total cholesterol >200 mg/dL	---	medium
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Smoking, current	---	high
Saigo_2001[123]	BMI ≥25 kg/m^2 versus <25 kg/m^2	multivariate logistic regression analysis of conventional coronary risk factors and hemostatic parameters	low
	DM (type 1 or type 2)		low
	Dyslipidemia, not specified		low
	Hypertension		low
	Smoking, current		medium
Sala_2001[124]	BMI ≥25 kg/m^2 versus <25 kg/m^2	E27 β_2-adrenergic receptor polymorphisms, age, smoking, DM, dyslipidemia, hypertension, and BMI	low
Sampaio_2007[125]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
	DM (type 1 or type 2)	---	medium
	LDL cholesterol, high, not specified	---	high
	Family history of cardiac disease	---	high
	Hypertension	---	medium
	Race (White versus other)	---	medium
	Smoking, current	---	high
Sandkamp_1990[126]	BMI ≥30 kg/m^2 versus <30 kg/m^2	---	medium
Sastry_2006[127]	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	high
	DM (type 1 or type 2)	---	high
	Dyslipidemia, not specified	---	high
	Hypertension	---	high
	Smoking	---	high
Schargrodsky_1994[128]	DM (type 1 or type 2)	---	high
	Family history of cardiac disease	---	high
	Hypertension	---	high
	Smoking, prior	---	high
	Smoking, current	---	high
Siegerink_2012[129]	DM (type 1 or type 2)	---	high
	Dyslipidemia, not specified	---	high
	Family history of cardiac disease	age (continuous), area of residence, year of event	medium
	Hypertension	---	high
	Race (White versus other)	---	medium
	Smoking, current	---	high
Singh_2010[130]	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	medium
	DM (type 1 or type 2)	---	high
	Hypertension	---	high
	Smoking, current	---	high

Study	Risk factor in meta-analysis	Covariates, if adjusted	Risk of bias
Sniderman_2016[33]	Total cholesterol, per SD change	age, sex, ethnicity, smoking, systolic blood pressure, diastolic blood pressure, and lipid-lowering medication	low
	HDL cholesterol, per SD change		low
	LDL cholesterol, per SD change		low
	Non-HDL cholesterol, per SD change		low
	Apo A1, per SD change		low
	Apo B, per SD change		low
Tanis_2006[131]	BMI ≥25 kg/m^2 versus <25 kg/m^2	---	medium
	C-reactive protein	age, index year, area of residence, DM, BMI, hypercholesterolemia	low
Vaccarino_2018[132]	Race (Black versus other)	---	medium
Walker_1967[133]	Family history of cardiac disease	---	high
	Hypertension	---	high
	Race (Black versus other)	---	medium
	Smoking, current	---	high
	Alcohol, current	---	high
Westover_2008[134]	BMI ≥30 kg/m^2 versus <30 kg/m^2	amphetamine abuse, cocaine abuse, tobacco, alcohol abuse, lipid disorder, hypertension, DM, obesity, congenital defects, coagulation defects	medium
	DM (type 1 or type 2)		medium
	Dyslipidemia, not specified		medium
	Hypertension, current		medium
	Smoking, current		medium
	Alcohol, current		medium
Yamac_2018[135]	Family history of cardiac disease	---	high
Yusuf_2004[20]	Obesity, waist-to-hip ratio	age, sex	low
	DM (type 1 or type 2)		medium
	ApoB/ApoA1, top versus lowest quintile		low
	Hypertension		medium
	Smoking, current		medium
	Alcohol, current		medium
Zoller_2015[136]	DM (type 1 or type 2)	age, sex, fetal growth, gestational age at birth, multiple birth, maternal and paternal education, cardiovascular and chromosomal anomalies or syndromes, DM, hypertension and parental history of ischemic heart disease	medium
	Family history of cardiac disease		medium
	Hypertension		medium
	Sex (males versus females)		low

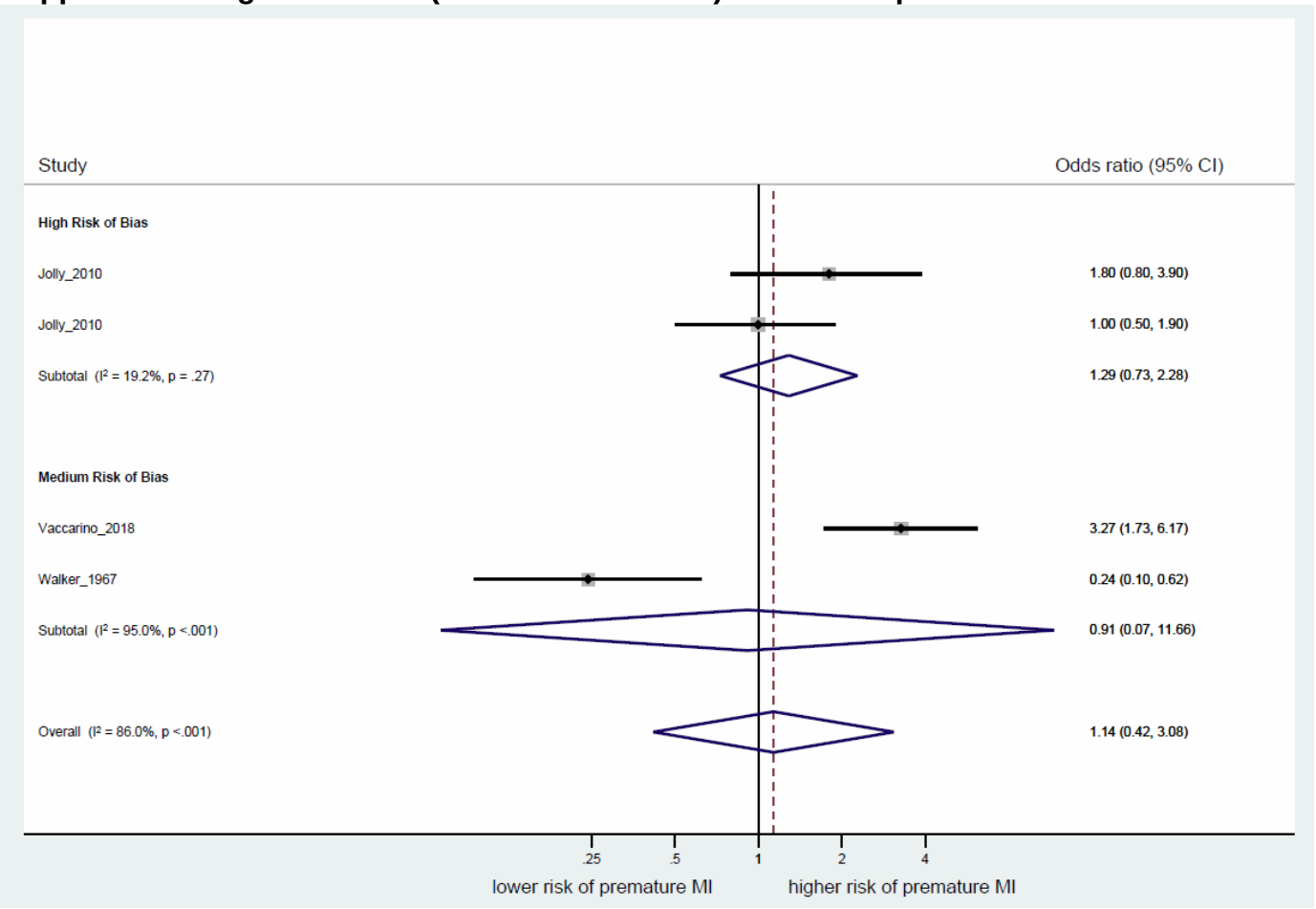
Abbreviations: apo: apolipoprotein; BMI: body-mass index; DM: diabetes mellitus; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; SD: standard deviation

Supplemental Table 7: Sex (men versus women) and risk of premature MI

	Reference	Risk of Bias	Men versus women odds ratio (95% CI)
	Celik_2008[73]	Low	1.76 (0.96−2.28)
	Roldan_2005[117]	Low	3.50 (2.19−5.62)
	Zoller_2015[136]	Low	2.33 (1.76−3.08)
Overall risk estimate			2.39 (1.71−3.35)
I^2 value; p-value			55.2%; p=.11

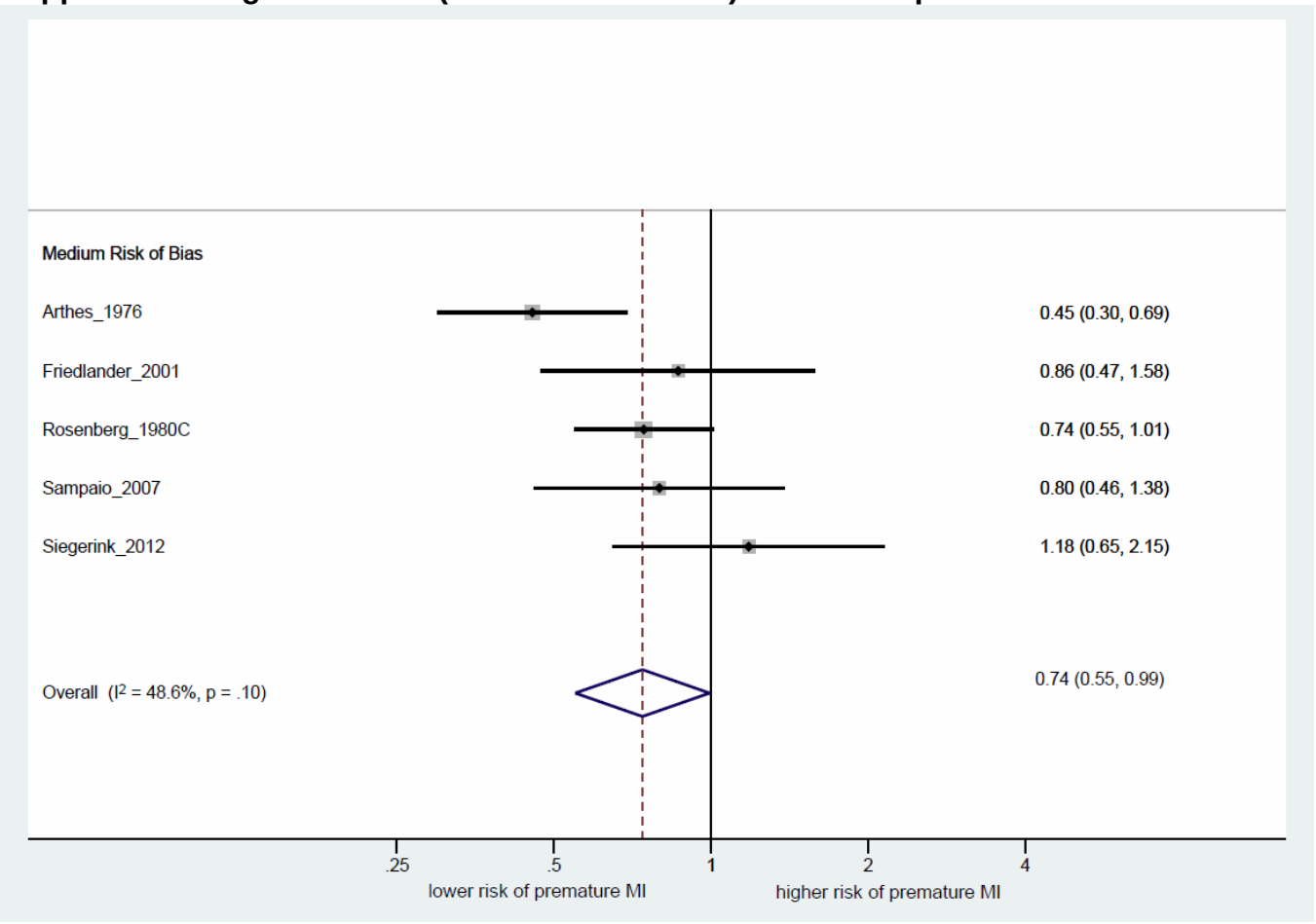
CI: confidence interval

Supplemental Figure 1: Race (Black versus other) and risk of premature MI



Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Figure 2: Race (White versus other) and risk of premature MI



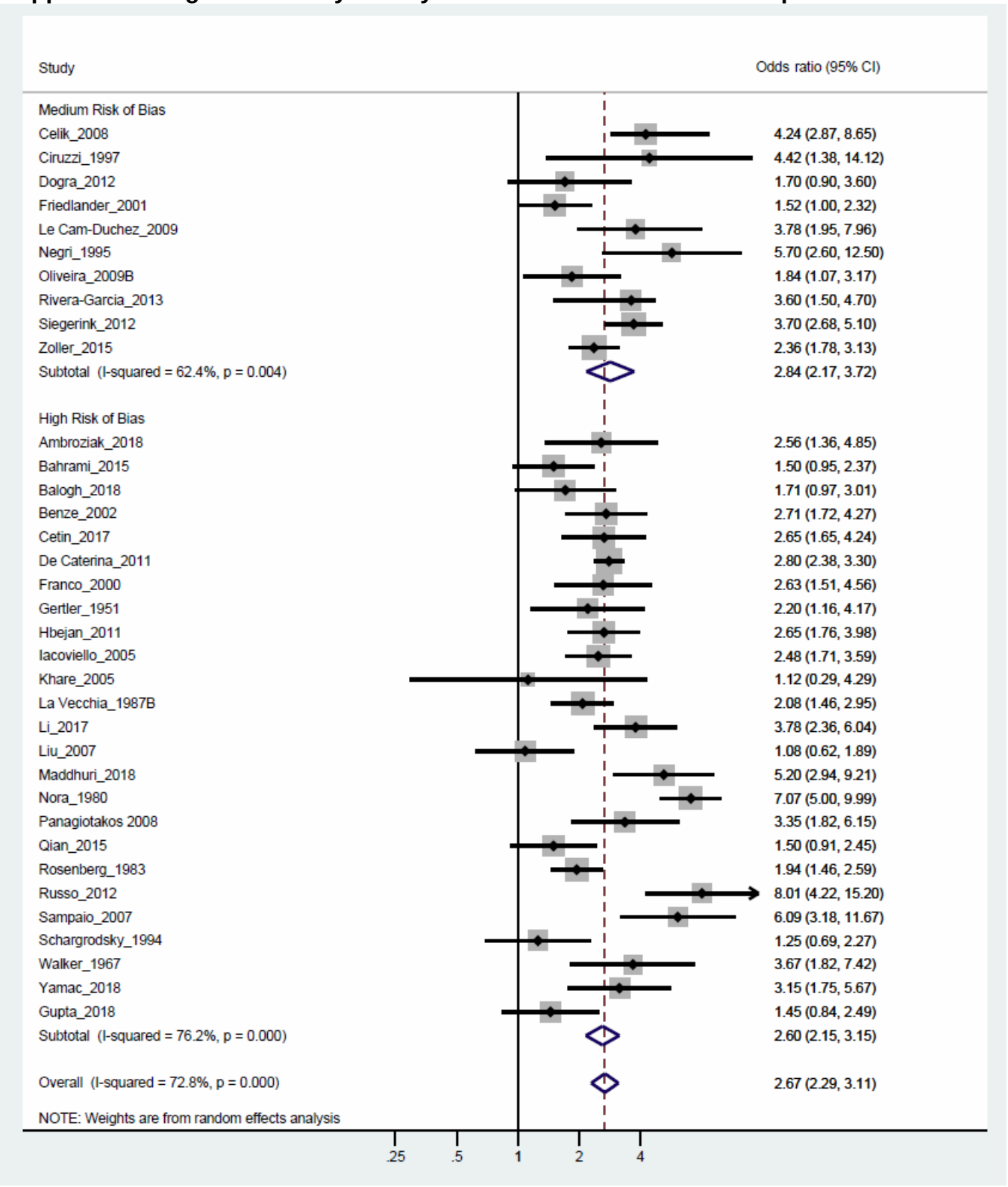
Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Table 8: Demographics and risk of premature MI, categorized by sex

Risk factor	Reference	Men OR (95% CI)	Reference	Women OR (95% CI)
Race (White versus other)			Arthes_1976[68]	0.45 (0.30–0.69)
			Friedlander_2001[84]	0.86 (0.47–1.58)
			Rosenberg_1980[118]	0.74 (0.55–1.01)
			Siegerink_2012[129]	1.18 (0.65–2.15)
Subtotal risk estimate				0.73 (0.51–1.06)
I^2 value; p-value				60.7%; p=0.05
Race (Black versus other)	Walker_1967[133]	0.24 (0.10–0.62)	Vaccarino_2018[132]	3.27 (1.73–6.17)
Family history of cardiac disease	Benze_2002[71]	2.71 (1.72–4.27)	Friedlander_2001[84]	1.52 (1.00–2.32)
	Hbejan_2011[89]	2.65 (1.76–3.98)	La Vecchia_1987[98]	2.08 (1.46–2.95)
	Li_2017[101]	3.78 (2.36–6.04)	Rosenberg_1983[120]	1.94 (1.46–2.59)
	Oliveira_2009[30]	1.84 (1.07–3.17)	Schargrodsky_1994[128]	1.25 (0.69–2.27)
	Walker_1967[133]	3.67 (1.82–7.42)	Siegerink_2012[129]	3.70 (2.68–5.10)
Subtotal risk estimate		2.80 (2.21–3.54)		2.02 (1.43–2.87)
I^2 value; p-value		11.8%; p=0.34		76.8%; p=0.002

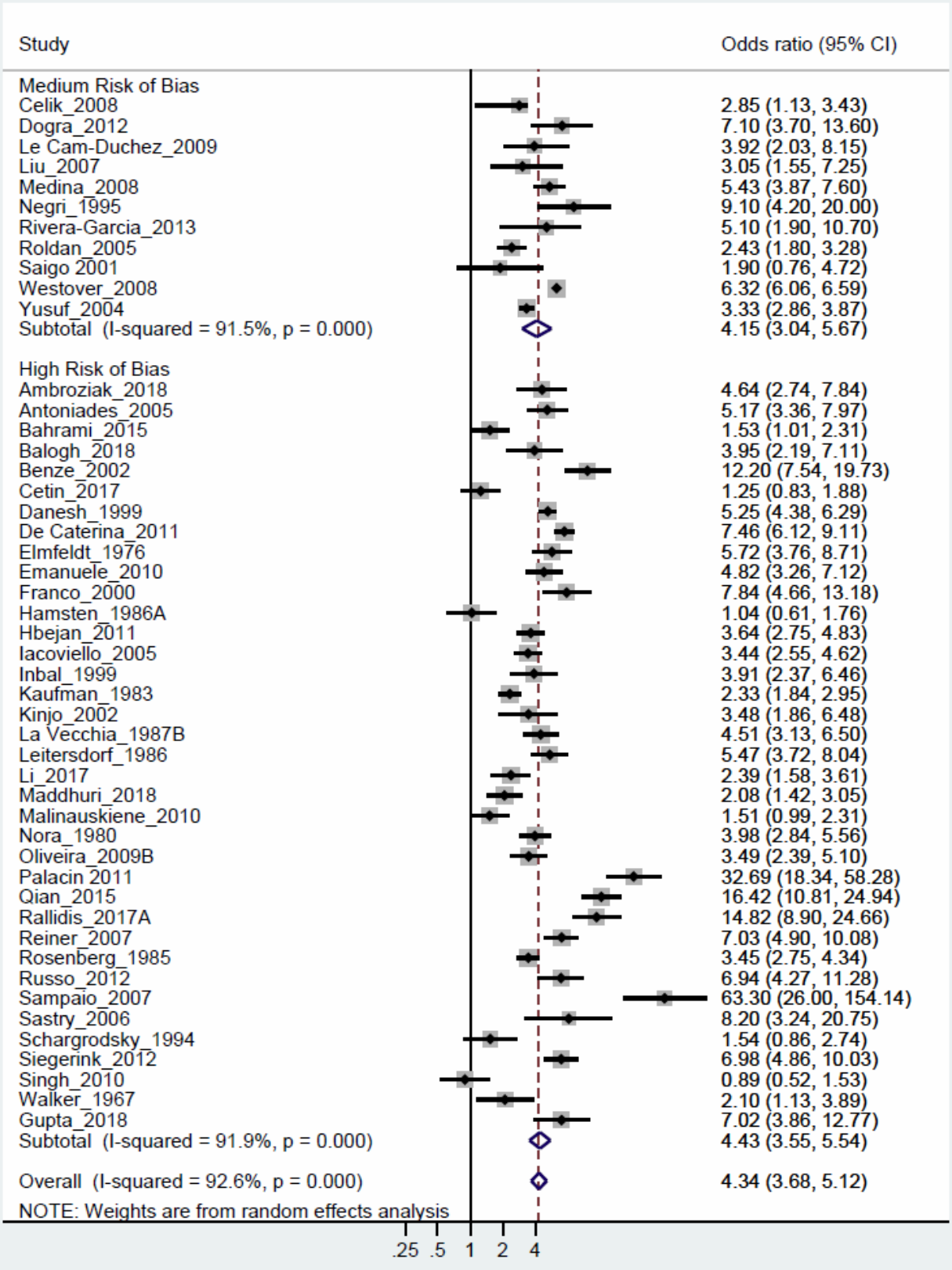
CI: confidence interval; MI: myocardial infarction; OR: odds ratio

Supplemental Figure 3: Family history of cardiac disease and risk of premature MI



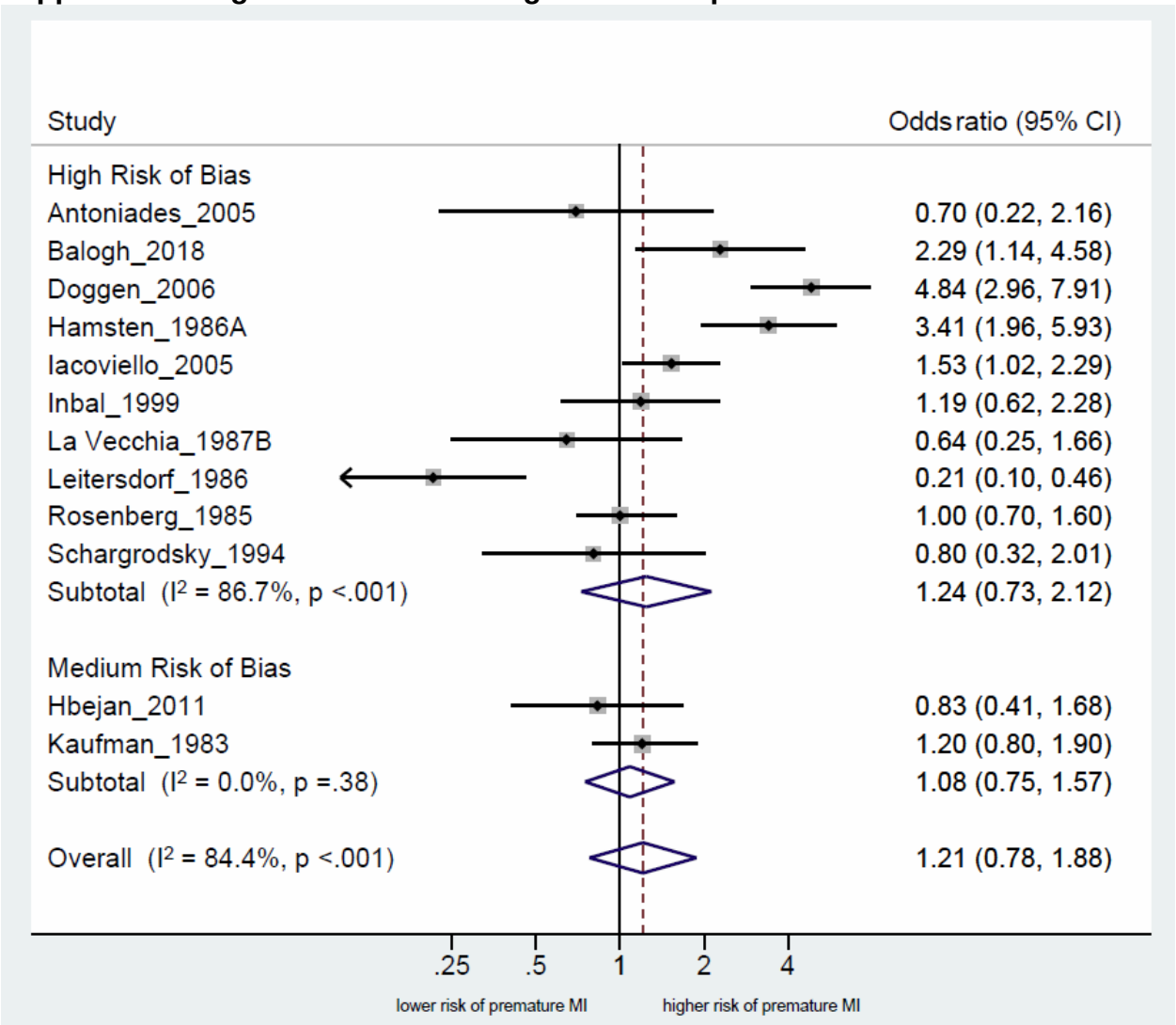
Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Figure 4: Current smoking and risk of premature MI



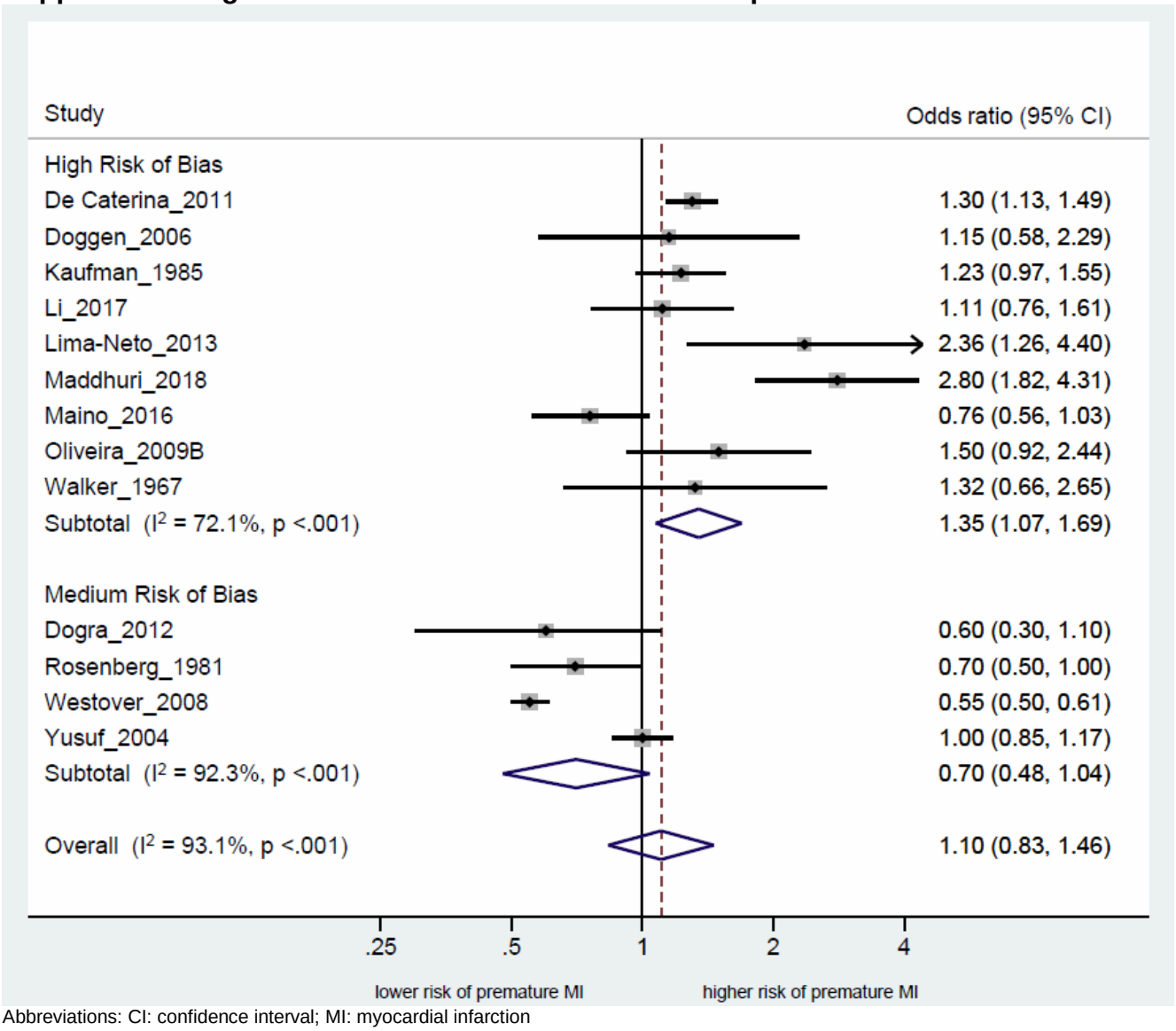
Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Figure 5: Prior smoking and risk of premature MI



Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Figure 6: Current alcohol use and risk of premature MI



Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Table 9: Prior alcohol use versus no/current and risk of premature MI

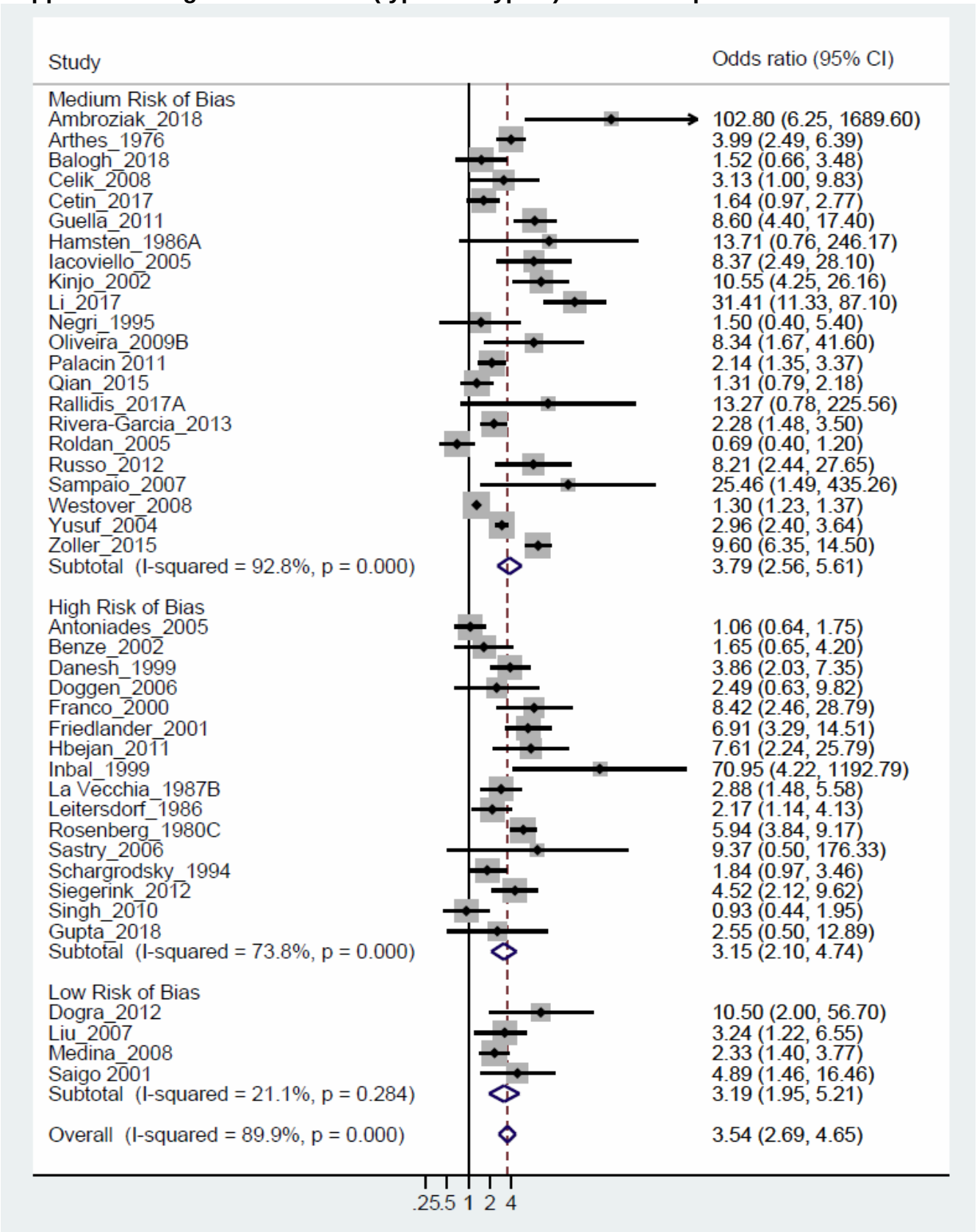
	Reference	Risk of Bias	Odds ratio (95% CI)
	Kaufman_1985[94]	Medium	0.70 (0.40−1.30)
	Rosenberg_1981[119]	Medium	0.80 (0.40−1.60)
Overall risk estimate			0.74 (0.47−1.16)
I^2 value; p-value			0%; p=.77

CI: confidence interval; MI: myocardial infarction

Supplemental Table 10: Lifestyle factors and risk of premature MI, categorized by sex

Risk factor	Reference	Men	Reference	Women
Smoking, current versus other	Benze_2002[71]	12.20 (7.54–19.73)	La Vecchia_1987[98]	4.51 (3.13–6.50)
	Elmfeldt_1976[81]	5.72 (3.76–8.71)	Malinauskiene_2010[106]	1.51 (0.99–2.31)
	Hamsten_1986[88]	1.04 (0.61–1.76)	Reiner_2007[115]	7.03 (4.90–10.08)
	Inbal_1999[91]	3.91 (2.37–6.46)	Rosenberg_1985[121]	3.45 (2.75–4.34)
	Kaufman_1983[93]	2.33 (1.84–2.95)	Schargrodsky_1994[128]	1.54 (0.86–2.74)
	Leitersdorf_1986[100]	5.47 (3.72–8.04)	Siegerink_2012[129]	6.98 (4.86–10.03)
	Li_2017[101]	2.39 (1.58–3.61)		
	Oliveira_2009[30]	3.49 (2.39–5.10)		
	Palacin_2011[111]	32.69 (18.34–58.28)		
	Saigo_2001[123]	1.90 (0.76–4.72)		
	Walker_1967[133]	2.10 (1.13–3.89)		
Subtotal risk estimate		4.01 (2.47–6.50)		3.56 (2.22–5.71)
I^2 value; p-value		92.5%; p<0.001		90.2%; p<0.001
Smoking, prior versus other	Doggen_2006[79]	4.84 (2.96–7.91)	La Vecchia_1987[98]	0.64 (0.25–1.66)
	Hamsten_1986[88]	3.41 (1.96–5.93)	Rosenberg_1985[121]	1.00 (0.70–1.60)
	Inbal_1999[91]	1.19 (0.62–2.28)	Schargrodsky_1994[128]	0.80 (0.32–2.01)
	Kaufman_1983[93]	1.20 (0.80–1.90)		
	Leitersdorf_1986[100]	0.21 (0.10–0.46)		
Subtotal risk estimate		1.42 (0.56–3.59)		0.91 (0.64–1.29)
I^2 value; p-value		92.8%; p<0.001		0.0%; p=0.68
Alcohol, current versus other	Doggen_2006[79]	1.15 (0.58–2.29)	Maino_2016[105]	0.76 (0.56–1.03)
	Kaufman_1985[94]	1.23 (0.97–1.55)	Rosenberg_1981[119]	0.70 (0.50–1.00)
	Li_2017[101]	1.11 (0.76–1.61)		
	Oliveira_2009[30]	1.50 (0.92–2.44)		
	Walker_1967[133]	1.32 (0.66–2.65)		
Subtotal risk estimate		1.23 (1.04–1.47)		0.73 (0.58–0.92)
I^2 value; p-value		0.0%; p=0.91		0.0%, p=0.74
Alcohol, prior versus other	Kaufman_1985[94]	0.70 (0.39–1.26)	Rosenberg_1981[119]	0.80 (0.40–1.60)
Alcohol, never versus other	Oliveira_2009[30]	2.21 (1.10–4.45)		

Supplemental Figure 7: Diabetes (type 1 or type 2) and risk of premature MI



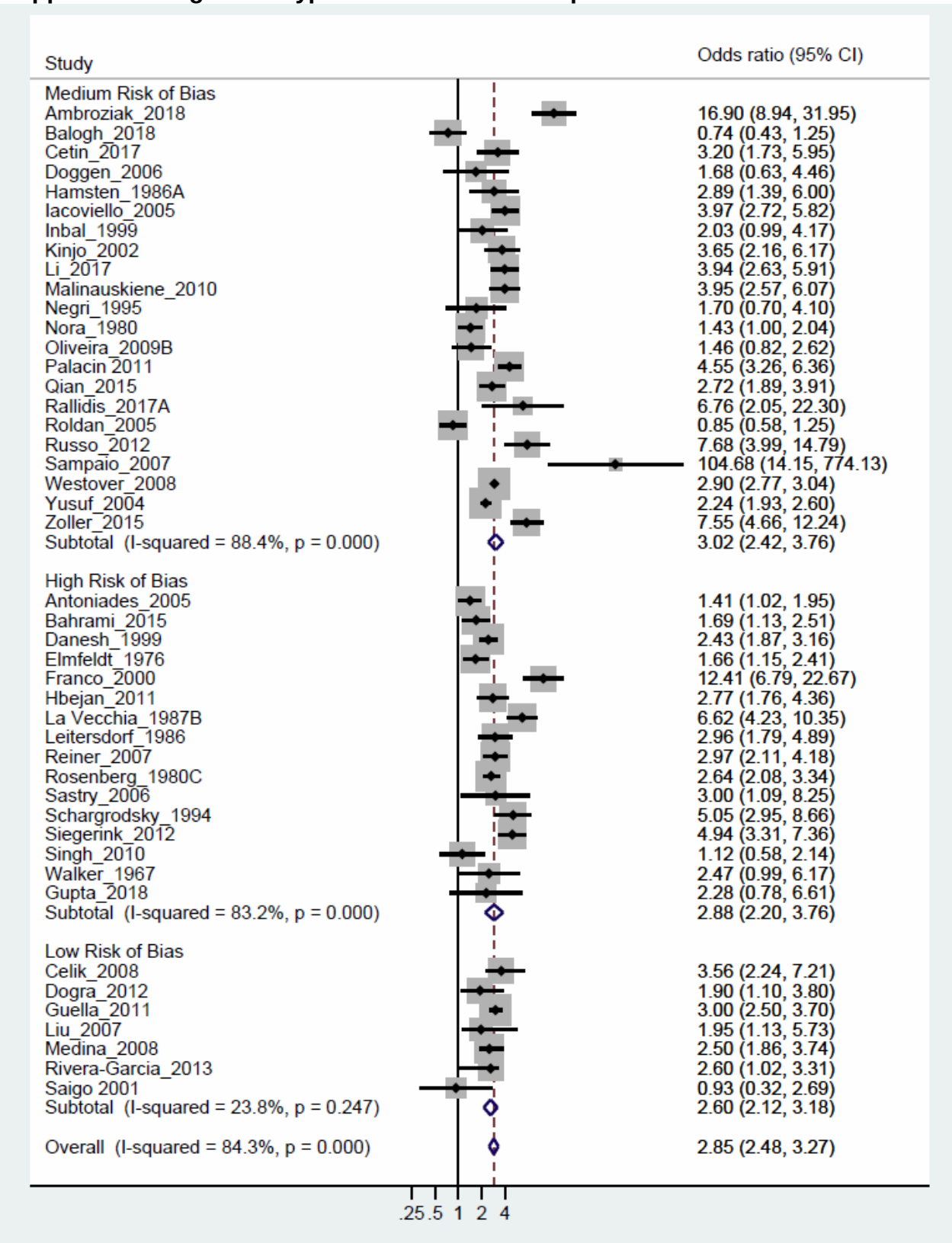
Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Table 11: Clinical risk factors and risk of premature MI, categorized by sex

Risk factor	Reference	Men	Reference	Women
DM (type 1 or type 2) (presence versus absence)	Benze_2002[71]	1.65 (0.65–4.20)	Arthes_1976[68]	3.99 (2.49–6.39)
	Doggen_2006[79]	2.49 (0.63–9.82)	Friedlander_2001[84]	6.91 (3.29–14.51)
	Hamsten_1986[88]	13.71 (0.76–246.17)	La Vecchia_1987[98]	2.88 (1.48–5.58)
	Hbejan_2011[89]	7.61 (2.24–25.79)	Rosenberg_1980[118]	5.94 (3.84–9.17)
	Inbal_1999[91]	70.95 (4.22–1192.79)	Schargrodsky_1994[128]	1.84 (0.97–3.46)
	Leitersdorf_1986[100]	2.17 (1.14–4.13)	Siegerink_2012[129]	4.52 (2.12–9.62)
	Li_2017[101]	31.41 (11.33–87.10)		
	Oliveira_2009[30]	8.34 (1.67–41.60)		
	Palacin_2011[111]	2.14 (1.35–3.37)		
	Saigo_2001[123]	4.89 (1.46–16.46)		
Subtotal risk estimate		5.04 (2.56–9.91)		3.99 (2.74–5.83)
I^2 value; p-value		74.3%; p<0.001		69.2%; p=0.03
Hypertension (presence versus absence)	Doggen_2006[79]	1.68 (0.63–4.46)	La Vecchia_1987[98]	6.62 (4.23–10.35)
	Elmfeldt_1976[81]	1.66 (1.15–2.41)	Malinauskiene_2010[106]	3.95 (2.57–6.07)
	Hamsten_1986[88]	2.89 (1.39–6.00)	Reiner_2007[115]	2.97 (2.11–4.18)
	Hbejan_2011[89]	2.77 (1.76–4.36)	Rosenberg_1980[118]	2.64 (2.08–3.34)
	Inbal_1999[91]	2.03 (0.99–4.17)	Schargrodsky_1994[128]	5.05 (2.95–8.66)
	Leitersdorf_1986[100]	2.96 (1.79–4.89)	Siegerink_2012[129]	4.94 (3.31–7.36)
	Li_2017[101]	3.94 (2.63–5.91)		
	Oliveira_2009[30]	1.46 (0.82–2.62)		
	Palacin_2011[111]	4.55 (3.26–6.36)		
	Saigo_2001[123]	0.93 (0.32–2.69)		
	Walker_1967[133]	2.47 (0.99–6.17)		
Subtotal risk estimate		2.45 (1.84–3.27)		4.01 (2.96–5.43)
I^2 value; p-value		65.7%; p=0.001		73.8%; p=0.002
Dyslipidemia, not specified (presence versus absence)	Doggen_2006[79]	3.16 (0.33–30.70)	La Vecchia_1987[98]	3.30 (1.95–5.60)
	Hbejan_2011[89]	2.76 (1.92–3.95)	Reiner_2007[115]	2.16 (1.55–3.01)
	Oliveira_2009[30]	1.48 (0.92–2.37)	Siegerink_2012[129]	4.78 (2.72–8.40)
	Palacin_2011[111]	1.61 (1.13–2.29)		
	Saigo_2001[123]	3.02 (1.31–6.98)		
Subtotal risk estimate		2.03 (1.47–2.80)		3.10 (1.93–5.00)
I^2 value; p-value		44.1%; p=0.13		67.5%; p=0.046
BMI ≥30kg/m^2 versus <30kg/m^2	Doggen_2006[79]	1.88 (1.03–3.40)	Malinauskiene_2010[106]	1.27 (0.84–1.93)
	Oliveira_2009[110]	2.05 (1.08–3.87)	Rosenberg_1983[120]	1.00 (0.50–1.70)
	Sandkamp_1990[126]	1.38 (0.92–2.07)	Choi_2018[75]	1.64 (0.91–2.96)
	Choi_2018[75]	2.31 (2.08–2.57)		
Subtotal risk estimate		1.94 (1.47–2.56)		1.28 (0.95–1.73)
I^2 value; p-value		51.4%; p=0.10		0.0%; p=0.52
BMI ≥25kg/m^2 versus <25kg/m^2	Doggen_2006[79]	1.14 (0.73–1.77)	La Vecchia_1987[97]	0.85 (0.47–1.55)
	Oliveira_2009[110]	1.65 (1.02–2.65)	Tanis_2006[131]	3.09 (2.09–4.57)
	Saigo_2001[123]	1.27 (0.50–3.25)	Choi_2018[75]	1.64 (0.91–2.96)
	Sala_2001[124]	1.26 (0.63–2.51)		
	Choi_2018[75]	2.31 (2.08–2.57)		
Subtotal risk estimate		1.94 (1.47–2.56)		1.28 (0.95–1.73)
I^2 value; p-value		51.4%; p=0.10		0%; p=0.52

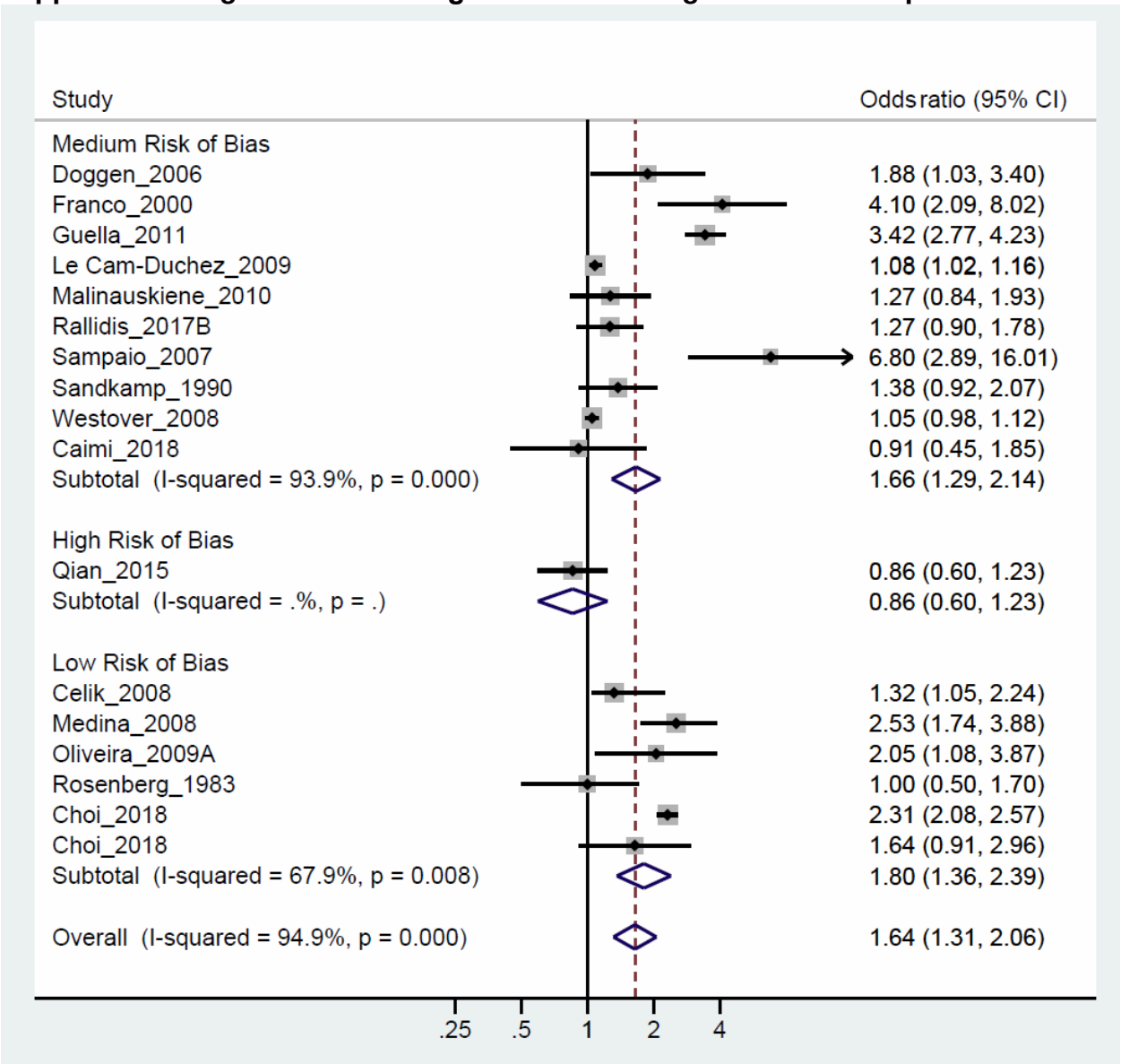
Abbreviations: BMI: body-mass index; DM: diabetes mellitus; CI: confidence interval; MI: myocardial infarction

Supplemental Figure 8: Hypertension and risk of premature MI



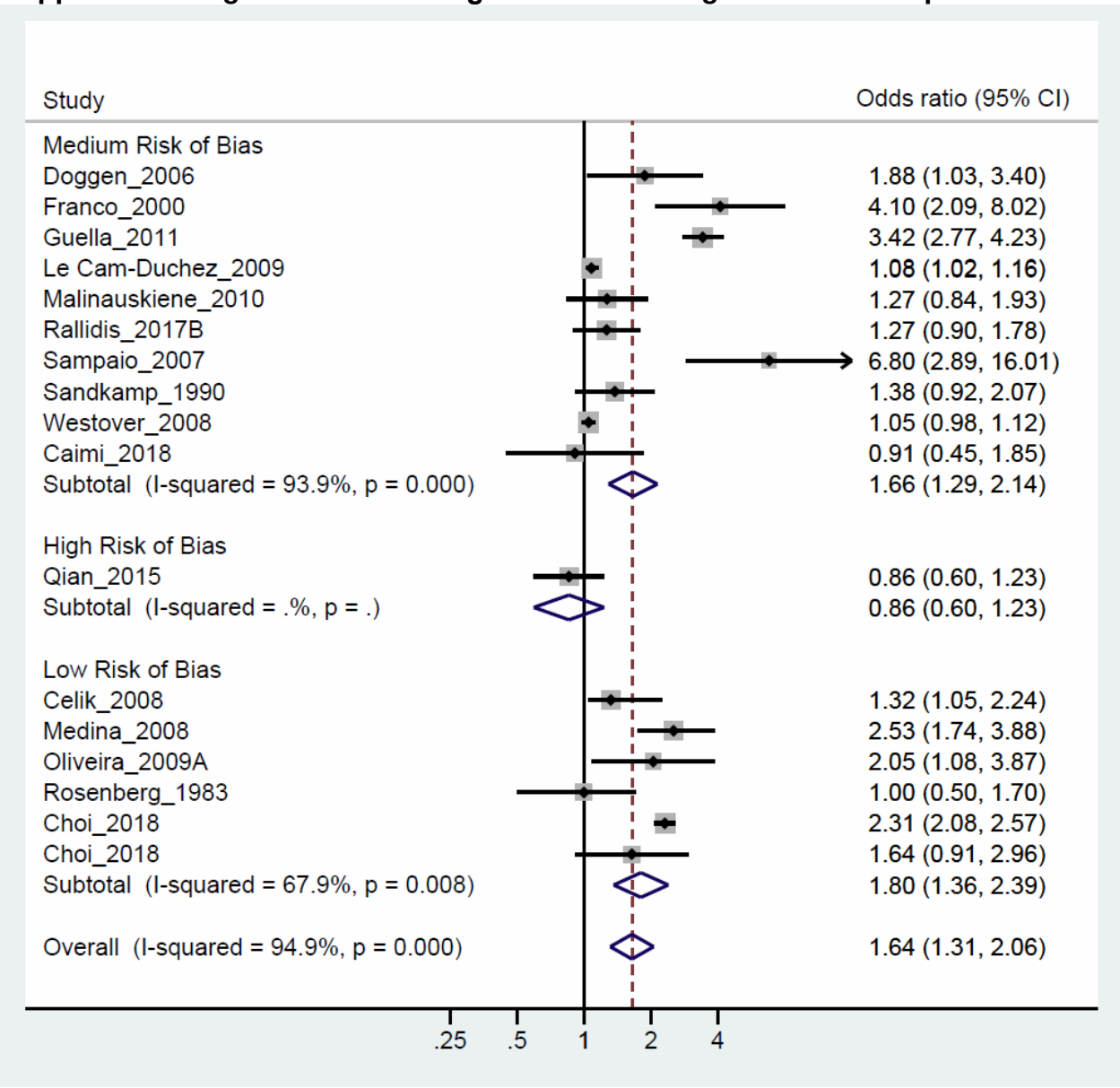
Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Figure 9: BMI ≥30kg/m^2 versus <30kg/m^2 and risk of premature MI



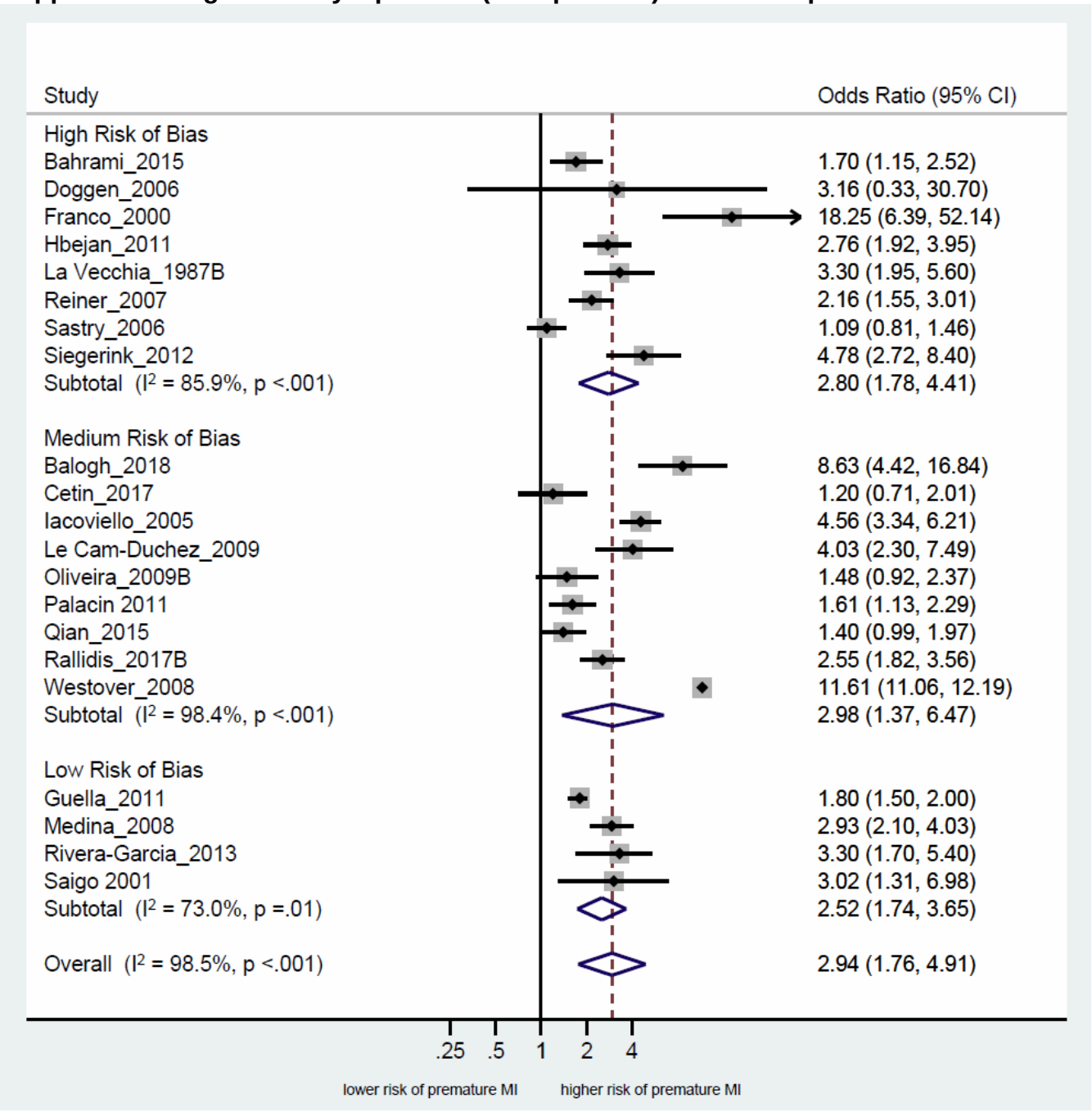
Abbreviations: BMI: body-mass index; CI: confidence interval; MI: myocardial infarction

Supplemental Figure 10: BMI ≥25kg/m^2 versus <25kg/m^2 and risk of premature MI



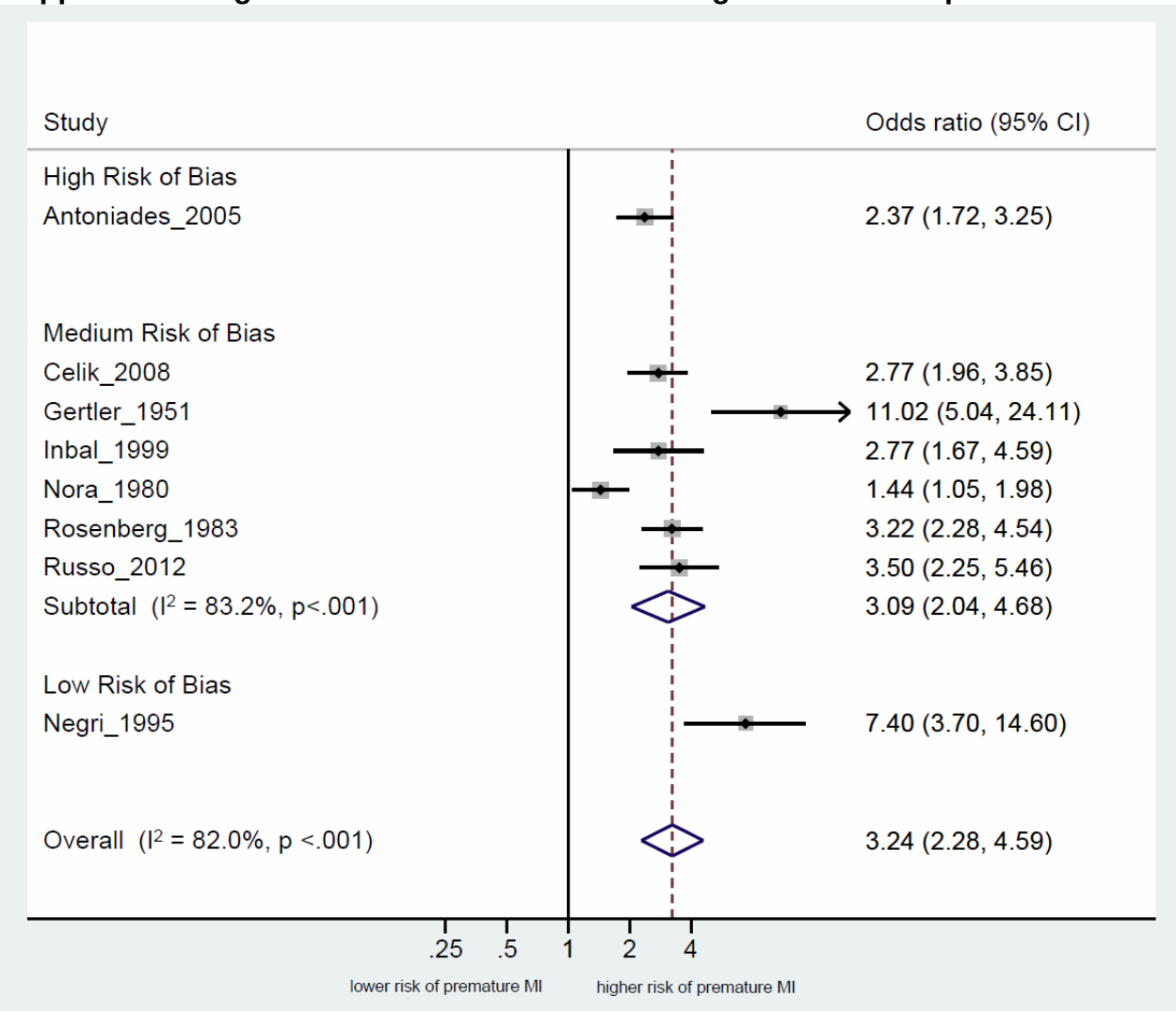
Abbreviations: BMI: body-mass index; CI: confidence interval; MI: myocardial infarction

Supplemental Figure 11: Dyslipidemia (not specified) and risk of premature MI



Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Figure 12: Total cholesterol >200 mg/dL and risk of premature MI



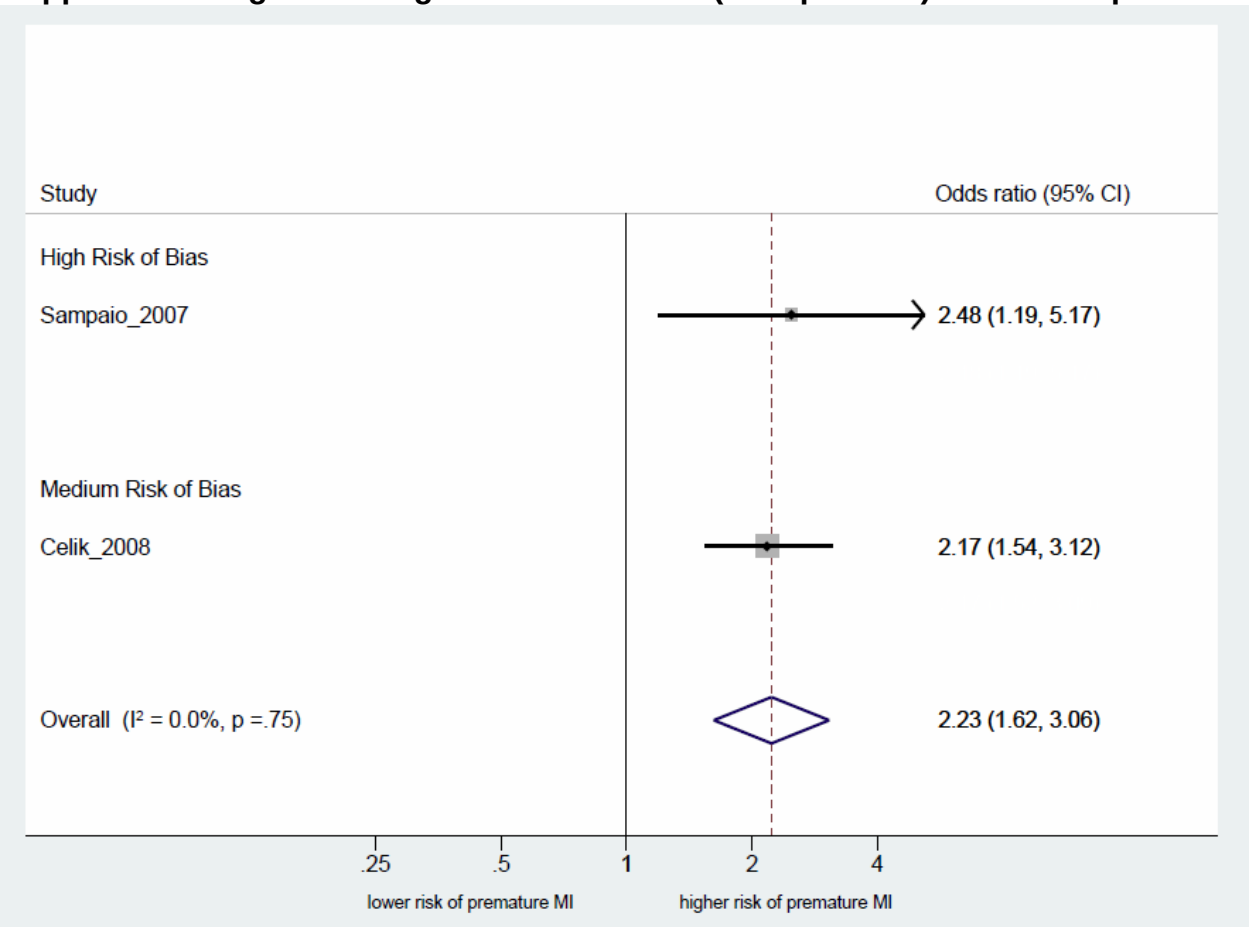
Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Table 12: HDL cholesterol <60 mg/dL and risk of premature MI

	Reference	Risk of Bias	Odds ratio (95% CI)
	Rosenberg_1983[120]	Medium	2.92 (1.70−5.00)
	Celik_2008[73]	Medium	2.99 (1.87−4.24)
Overall risk estimate			2.96 (2.14−4.11)
I^2 value; p-value			0%; p=.94

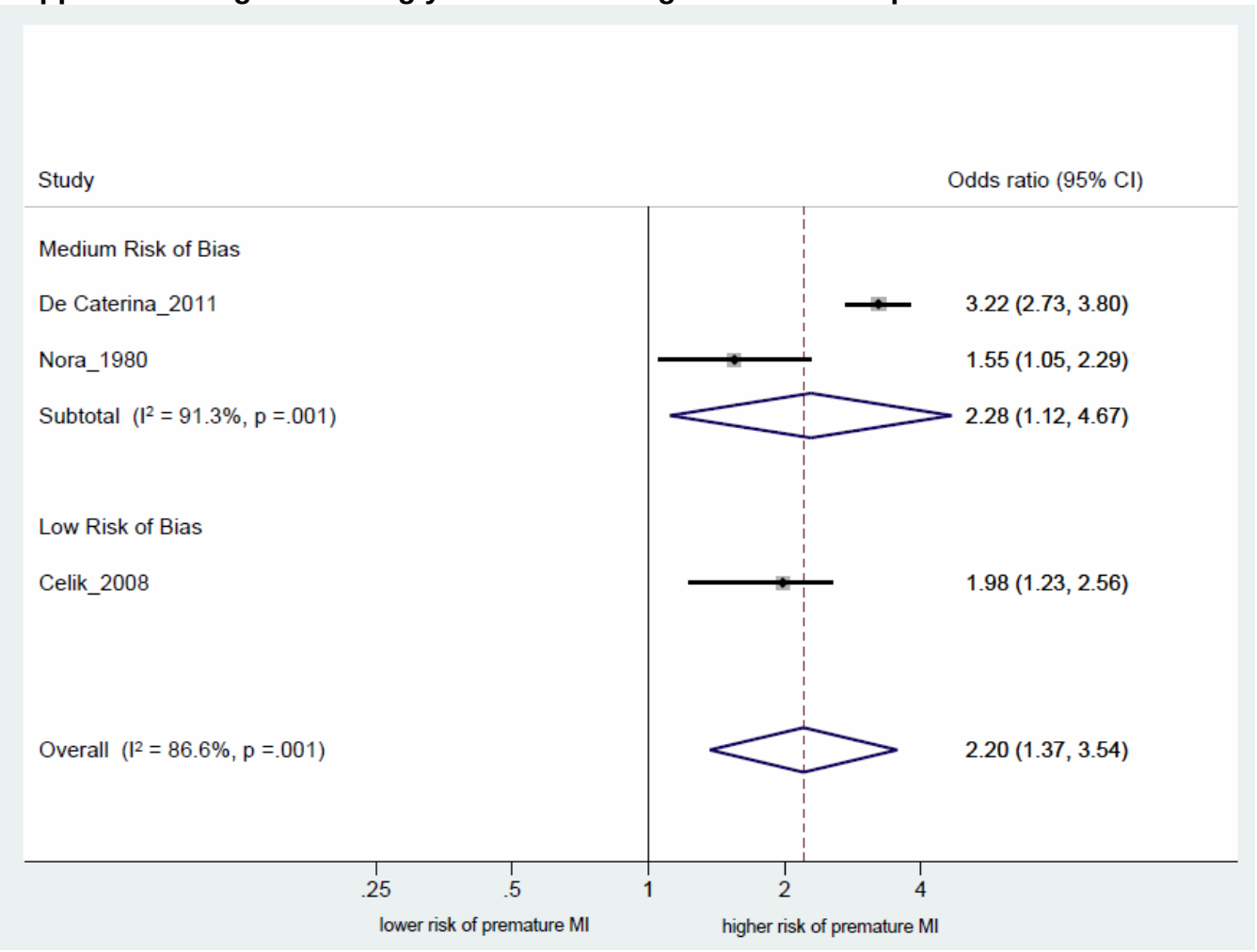
CI: confidence interval; MI: myocardial infarction

Supplemental Figure 13: High LDL cholesterol (not specified) and risk of premature MI



Abbreviations: CI: confidence interval; LDL: low-density lipoprotein; MI: myocardial infarction

Supplemental Figure 14: Triglycerides >150 mg/dL and risk of premature MI



Abbreviations: CI: confidence interval; MI: myocardial infarction

Supplemental Table 13: Lipids (per SD increment) and risk of premature MI

Risk factor	Reference	Age category (years)	Risk of Bias	Odds ratio (95% CI) per SD increment
LDL cholesterol	Sniderman_2016[33]	age <40	Low	1.38 (1.23−1.55)
		40≤ age <50	Low	1.55 (1.44−1.57)
Overall risk estimate				1.48 (1.32−1.65)
I^2 value; p-value				63.6%; p=.10
HDL cholesterol	Sniderman_2016[33]	age <40	Low	0.87 (0.76−0.99)
		40≤ age <50	Low	0.87 (0.80−0.94)
Overall risk estimate				0.87 (0.81−0.93)
I^2 value; p-value				0%; p=1.0
Non-HDL cholesterol	Sniderman_2016[33]	age <40	Low	1.32 (1.18−1.48)
		40≤ age <50	Low	1.47 (1.37−1.58)
Overall risk estimate				1.41 (1.27−1.56)
I^2 value; p-value				59.7%; p=.12
Apolipoprotein A1	Sniderman_2016[33]	age <40	Low	0.70 (0.64−0.75)
		40≤ age <50	Low	0.66 (0.57−0.76)
Overall risk estimate				0.69 (0.64−0.74)
I^2 value; p-value				0%; p=.48
Apolipoprotein B	Sniderman_2016[33]	age <40	Low	1.62 (1.51−1.74)
		40≤ age <50	Low	1.51 (1.34−1.70)
Overall risk estimate				1.59 (1.50−1.69)
I^2 value; p-value				0%; p=.32

CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; SD: standard deviation

Supplemental Table 14: Lipids and risk of premature MI

Risk factor	Reference	Risk of Bias	Hazard ratio (95% CI) top vs. lowest quartile
Total cholesterol	Lee_2020[34]	Medium	2.01 (1.97−2.22)
HDL cholesterol	Lee_2020[34]	Medium	0.49 (0.46−0.52)
LDL cholesterol	Lee_2020[34]	Medium	1.47 (1.38−1.56)
Triglycerides	Lee_2020[34]	Medium	2.48 (2.33−2.64)

CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction;

Supplemental Table 15: Biomarkers and risk of premature MI, categorized by sex

Risk factor	Reference	Men	Reference	Women
Total cholesterol >200 mg/dL versus ≤200 mg/dL	Inbal_1999[91]	2.77 (1.67–4.59)	Rosenberg_1983[120]	3.22 (2.28–4.54)
HDL cholesterol <60 mg/dL versus ≥60 mg/dL			Rosenberg_1983[120]	2.92 (1.70–5.00)
HDL/total cholesterol ratio, per 0.1 drop			Montes_2005[32]	1.40 (0.90–2.20)
CRP 0.5–1.34 mg/L versus <0.5 mg/L			Tanis_2006[131]	0.50 (0.27–0.91)
CRP 1.34–4.97 mg/L versus <0.5 mg/L			Tanis_2006[131]	0.80 (0.46–1.39)
CRP ≥4.9 mg/L versus <0.5 mg/L			Tanis_2006[131]	1.00 (0.51–1.95)

Abbreviations: CRP: C-reactive protein; HDL: high-density lipoprotein; MI: myocardial infarction