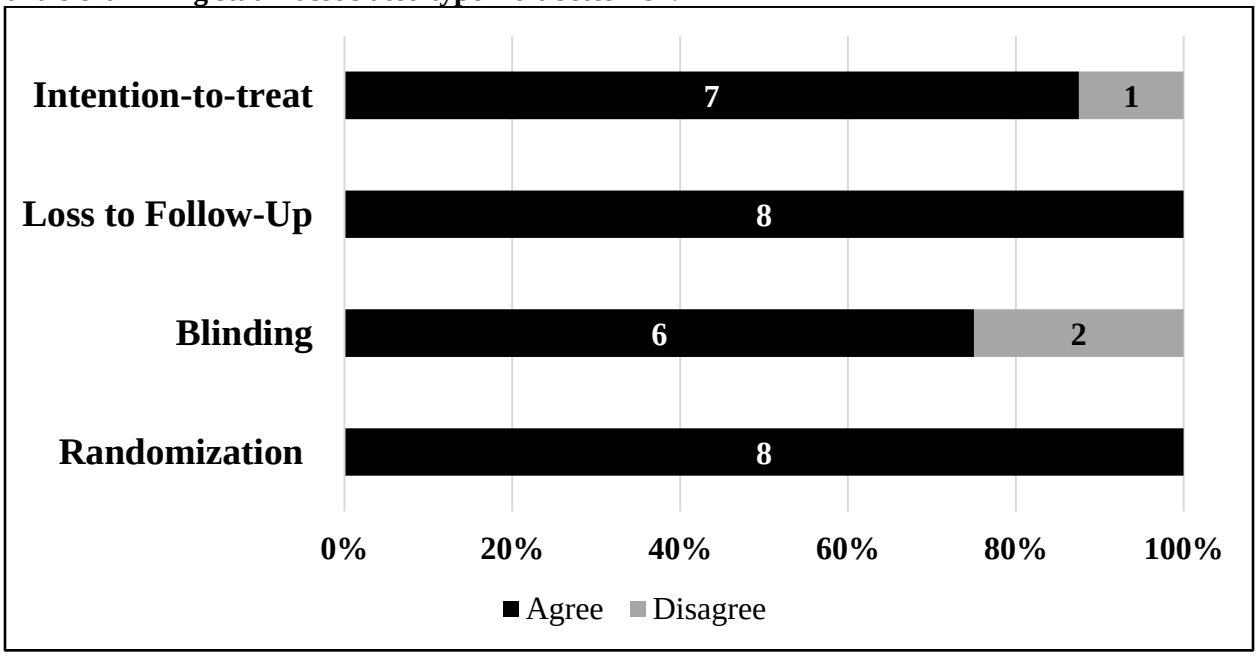
SUPPLEMENTAL MATERIAL

I. Risk of bias among observational studies

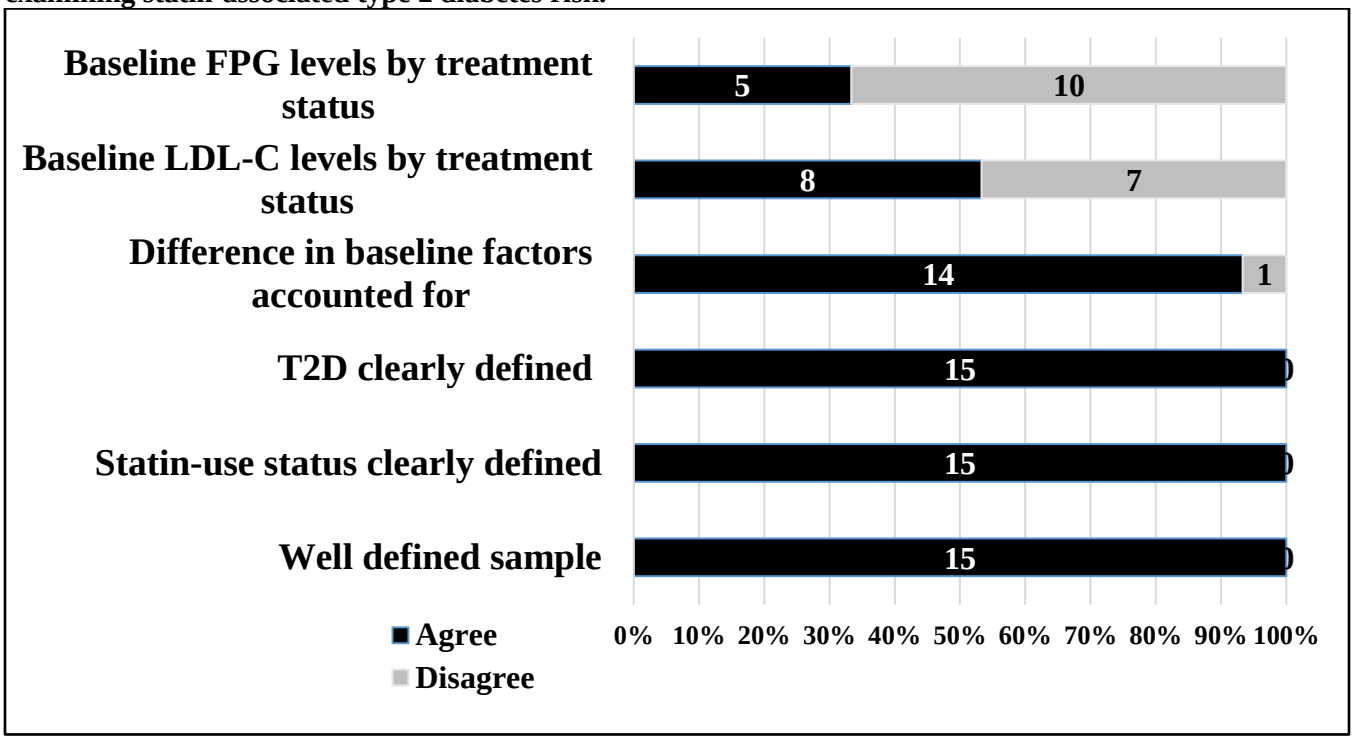
To further assess the risk of bias among observational studies (OBSs), we used the average standardized absolute mean difference (ASAMD) to assess balance between statin-treated and comparison groups, with lower ASAMD indicating better balance.[1] Balance was assessed across covariates selected based on past evidence and theory. ASAMD was calculated by subtracting each of the comparison group means from the corresponding statin-treated group mean, taking the absolute value of each difference, dividing each absolute difference by the pooled standard deviation of the covariate (if continuous), and then computing the mean of the standardized absolute differences.[1]

II. Supplemental figures

Supplemental Figure 1. Summary of quality assessment for included eight randomized controlled trials examining statin-associated type 2 diabetes risk.

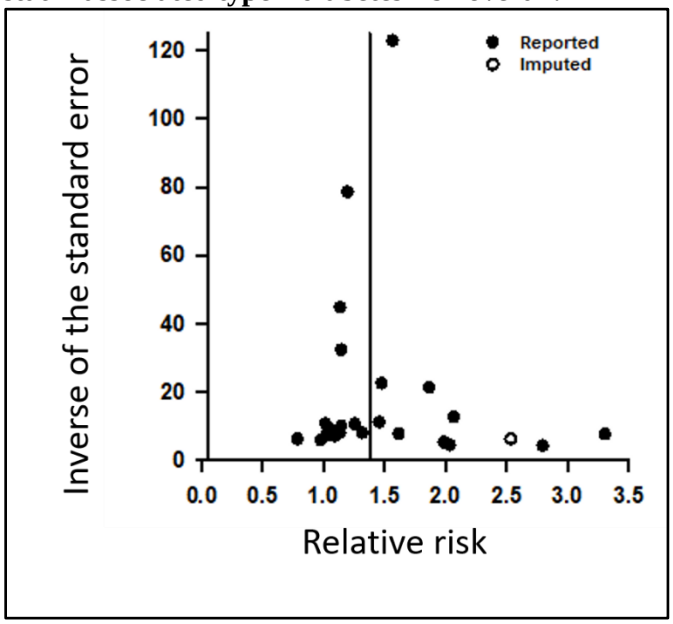


Supplemental Figure 2. Summary of quality assessment for included 15 observational studies examining statin-associated type 2 diabetes risk.

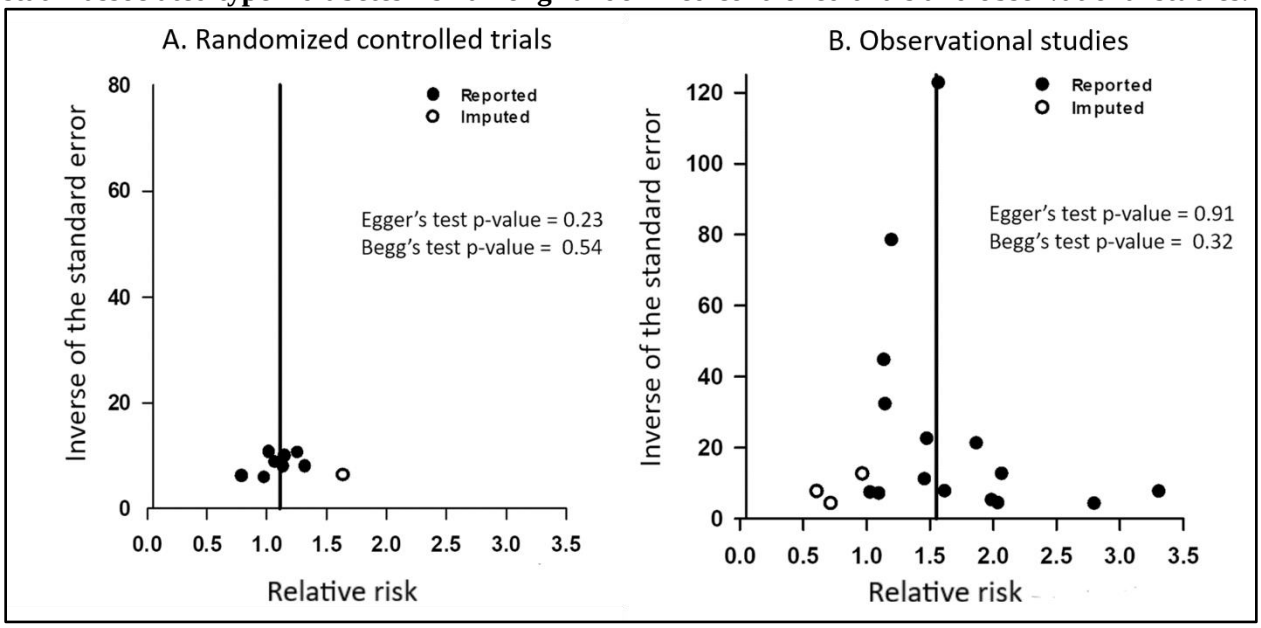


FPG = Fasting plasma glucose
LDL-C = Low-density lipoprotein
T2D = Type 2 diabetes

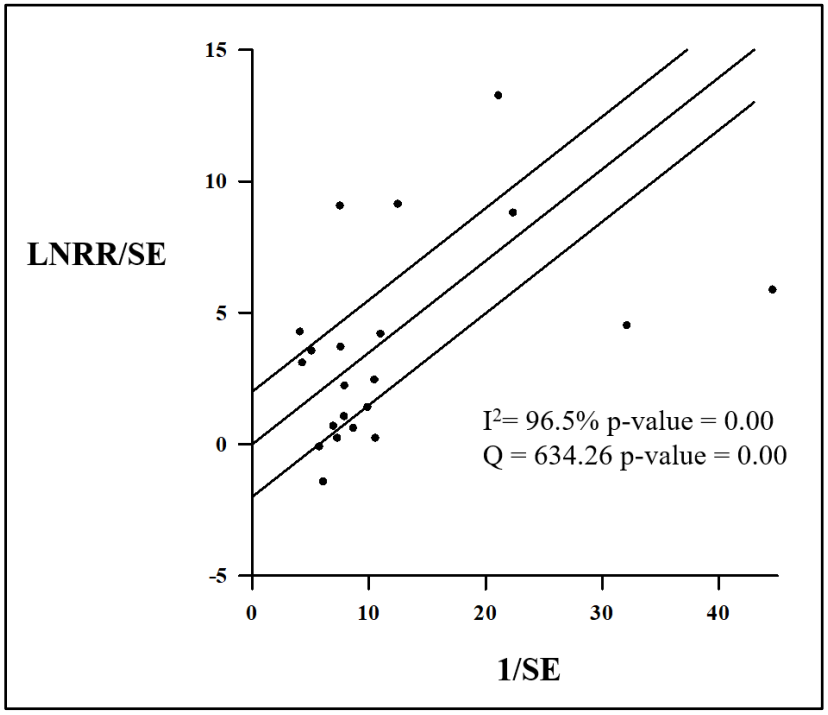
Supplemental Figure 3. Funnel plot displaying reported and imputed relative risks examining statin-associated type 2 diabetes risk overall.



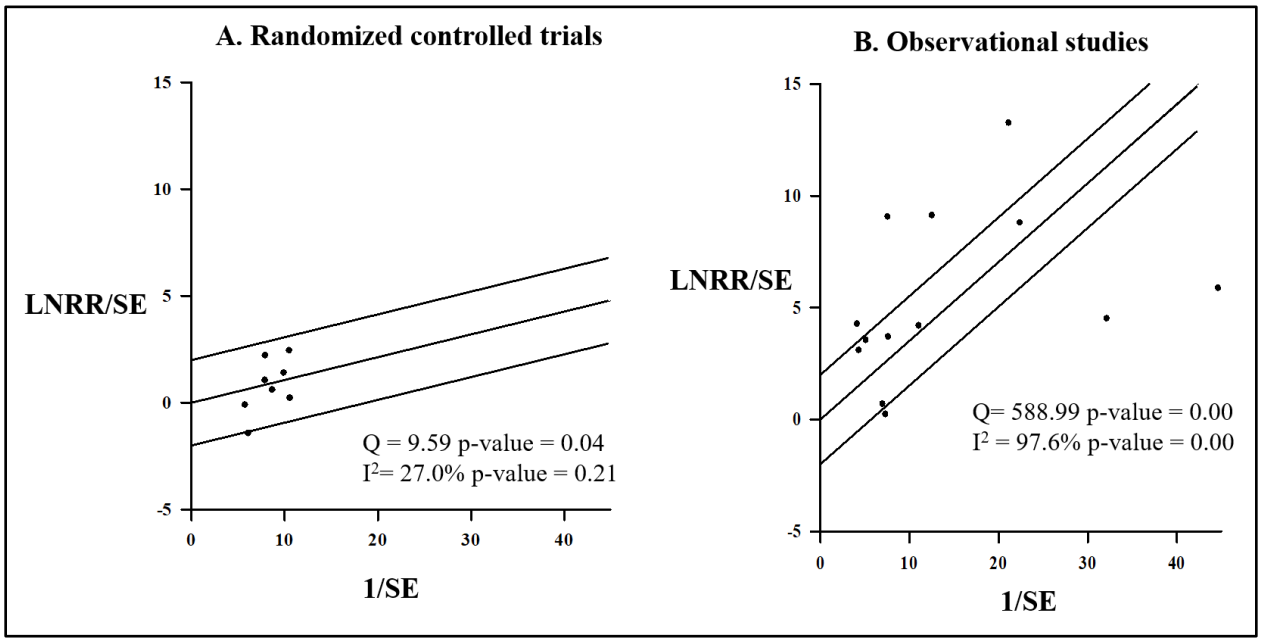
Supplemental Figure 4. Funnel plots displaying reported and imputed relative risks examining statin-associated type 2 diabetes risk among randomized controlled trials and observational studies.



Supplemental Figure 5. Galbraith plot displaying relative risks examining statin-associated type 2 diabetes risk and 95% confidence intervals overall.



Supplemental Figure 6. Galbraith plot displaying relative risks examining statin-associated type 2 diabetes risk and 95% confidence intervals among randomized controlled trials and observational studies.



III. Supplemental tables

Supplemental Table 1. Study and baseline participant characteristics abstracted from 23 studies examining statin-associated type 2 diabetes risk.

Study characteristics
Study design (randomized controlled trials cohort, case-control, cross sectional)
Mean length of follow-up time
Study sample size
Year of publication data
Year of study baseline
Method to control confounding (propensity score, adjusted in the model, randomization, did not adjust)
Methods to measure and define type 2 diabetes status (physician diagnosis, medication data, laboratory data)
Type of effect estimate metric (odds ratio, relative risk, hazard ratio)
Participant characteristics
% Female
Mean Age (10-year age groups)
% Caucasian
Residence of participant
% prescribed statins
Type of statins included
Mean BMI
Mean LDL-C levels
Mean fasting plasma glucose levels
Mean systolic blood pressure levels
% hypertensive
% current smokers
% of population with ASCVD at baseline

Supplemental Table 2. Additional characteristics of interest among eight randomized controlled trials examining statin-associated type 2 diabetes risk.

	Study characteristics			Participant characteristics				
Studies	Type of effect estimate	Residence of participant	Type of statin	% prescribed statins	Mean systolic blood pressure levels (mmHG)	% Hypertensive	% Current smokers	% of populations with ASCVD at baseline
Downs (1998)[2]	RR	North America	Lovastatin	49.8	138	22	12.5	0
Freeman (2001)[3]	HR	Europe	Pravastatin	50	135	16	43	0
Furberg (2002)[4]	RR	North America	Pravastatin	49.6	145	100	23.2	14
Shepherd (2002)[5]	HR	Europe	Pravastatin	50	154.6	61.9	26.8	44.2
Sever (2003)[6]	HR	Europe	Atorvastatin	50	164.2	100	32.7	11
Nakamura (2006)[7]	HR	Asia	Pravastatin	49.5	132.25	40.9	15.4	0
Ridker (2008)[8]	HR	Multiple	Rosuvastatin	50	134	NA	15.8	0
Yusuf (2016)[9]	HR	Multiple	Rosuvastatin	50	137.9	37.8	26.8	0

8 studies (1998-2016)	50	142.6	54.1	24.5	8.7

ASCVD = Atherosclerotic cardiovascular disease

Supplemental Table 3. Additional characteristics of interest among 15 observational studies examining statin-associated type 2 diabetes risk.

	Study characteristics		Participant characteristics					
Studies	Type of effect estimate	Method to deal with confounding	Residence of participant	% prescribed statins*	Mean systolic blood pressure levels (mmHG)	% Hypertensive	% Current smokers	% of populations with ASCVD at baseline
Jick (2004)[10]	OR	Controlled	Europe	22.0	NA	40.23	22.2	0.0
Culver (2012)[11]	HR	Controlled	North America	7.0	NA	NA	7.0	15.9
Wang (2012)[12]	HR	Unadjusted	Asia	20.0	NA	NA	NA	47.0
Danaei (2012)[13]	HR	Controlled	Europe	4.9	NA	51.3	42.1	0.0
Izzo (2013)[14]	HR	Controlled	Europe	14.0	141.8	NA	NA	0.0
Chen (2013)[15]	OR	Controlled	Asia	3.8	NA	4.0	NA	4.0

Currie (2013)[16]	HR	Controlled	Oceania	39.3	NA	NA	NA	NA
Zaharan (2013)[17]	HR	Controlled	Europe	13.5	NA	NA	NA	5.0
Macedo (2014)[18]	HR	Propensity scores	Europe	21.4	NA	26.2	17.7	36.0
Bhattacharya (2014)[19]	OR	Controlled	North America	50.0	NA	NA	18.5	10.0
Cederberg (2014)[20]	HR	Controlled	Europe	NA	NA	NA	NA	12.0
Mansi (2015)[21]	OR	Propensity scores	North America	50.0	NA	35.4	6.2	0.0
Radford (2015)[22]	OR	Controlled	North America	14.3	NA	12.3	12	0.0
Olotu (2016)[23]	OR	Propensity scores	North America	50.0	NA	17.3	NA	NA
Rha (2016)[24]	OR	Propensity scores	Asia	21.0	NA	53.0	NA	13.0
15 studies (2004-2016)				23.7	141.8	30.0	18.0	11.0

*****All OBSs included multiple statins
ASCVD = Atherosclerotic cardiovascular disease

Supplemental Table 4. Results from meta-regression models among 23 randomized controlled trials and observational studies examining statin-associated type 2 diabetes risk.

Characteristics	N	Relative risk (95% CI)	P-value
Study characteristics			
Study design	23		
Randomized controlled trials	8	Ref	
Observational studies	15	1.45 (1.11-1.88)	0.01*
Mean length of follow-up	23	0.99 (0.96-1.03)	0.71
Sample size	23	1 (0.99,1.00)	0.92
Year of publication	23	1.03 (1.00-1.06)	0.01*
Year of baseline	23	1.02(0.99-1.05)	0.10
Methods address confounders	23		
Randomization	8	Ref	
Controlled	10	1.40 (1.05-1.85)	0.03*
Propensity or unadjusted	5	1.53 (1.01-2.15)	0.02*
Type of effect estimate metric	23		
Hazard ratio	16	Ref	
Relative risk or odds ratio	7	1.12 (0.81-1.56)	0.48
Methods to measure and define T2D	23		
Physician report, medication use, lab results	6	Ref	
2 out of 3 methods	9	1.25 (0.88-1.79)	0.20
1 out of 3 methods or self-report	8	1.40 (0.97-2.01)	0.07
Participant characteristics			
Residence of participants	23		
Europe	9	Ref	
North America	7	1.30 (0.93-1.82)	0.12
Other	7	1.30 (0.92-1.83)	0.13
% Women	23	1.49 (0.81-2.76)	0.19
Mean age (10-year increase)	21	0.79 (0.63-0.98)	0.04*
% Caucasian	21	0.88 (0.59-1.32)	0.52
Proportion taking statins	22		
>30%	12	Ref	
<30%	10	1.03 (0.76-1.39)	0.85
Mean BMI (kg/m^2)	15	0.98 (0.90-1.07)	0.69

Mean LDL-C levels (10-mg/dl increase)	15	0.92 (0.87-0.97)	<0.01*
Mean plasma glucose levels (10-mg/dl increase)	12	0.98 (0.83-1.16)	0.80
Mean systolic blood pressure levels (10-mmHG increase)	9	1.00 (0.99-1.02)	0.37
% Hypertensive	15	0.68 (0.34-1.33)	0.23
% Current smokers	15	0.27 (0.11-0.68)	0.01*
% ASCVD	21	1.23 (0.54-2.78)	0.61

*P-value <0.05
FPG = Fasting plasma glucose
BMI = Body mass index
LDL-C = Low-density lipoprotein cholesterol
ASCVD = Atherosclerotic cardiovascular disease

Supplemental Table 5. Results from meta-regression models among 15 observational studies examining statin-associated type 2 diabetes risk.

Characteristics	N	Relative risk (95% CI)	P-value
Study characteristics			
Mean length of follow-up	15	0.98 (0.94, 1.02)	0.24
Sample size	15	0.99 (0.99-1)	0.56
Year of publication	15	1.05 (0.99-1.12)	0.12
Year of baseline	15	1.02 (0.99-1.06)	0.20
Type of effect estimate metric	15		
Hazard ratio	10	Ref	
Odds ratio	5	1.16 (0.76-1.76)	0.47
Methods to measure and define T2D	15		
Used 1 method (physician report, lab results, medication use)	6	Ref	
Used > 1 method	9	0.96 (0.64-1.43)	0.83
Use of FPG to define T2D	15		
Not used	11	Ref	
Used	4	0.95 (0.60-1.51)	0.83
Participant characteristics			
Residence of participants	15		
Europe	6	Ref	
Other	9	1.50 (1.11-2.04)	0.01*
% Women	15	1.12 (0.48-2.59)	0.78
Mean age (10-year increase)	13	0.71 (0.52-0.96)	0.03*
% Caucasian	13	0.75 (0.43-1.28)	0.26
Proportion taking statins	15		
>30%	5	Ref	
<30%	10	0.71 (0.50-1.10)	0.06
Mean BMI (kg/m^2)	7	0.84 (0.70-1.01)	0.06
Mean LDL-C levels (10-mg/dl increase)	7	0.78 (0.67-0.92)	0.01*
Mean glucose levels (10-mg/dl increase)	5	0.89 (0.27-2.95)	0.78
% Hypertensive	8	0.28 (0.07-1.04)	0.06
% Current smokers	7	0.31 (0.11-0.87)	0.03*
% ASCVD	13	0.85 (0.28-2.61)	0.76
Type of statin user			
Prevalent User	12	Ref	
New User	3	1.14 (0.70-1.82)	0.56

*P-value <0.05

BMI = Body mass index
LDL-C = Low-density lipoprotein cholesterol
FPG = Fasting plasma glucose
ASCVD = Atherosclerotic cardiovascular disease

Supplemental Table 6. Results from meta-regression models among eight randomized controlled trials examining statin-associated type 2 diabetes risk.

Characteristics	N	Relative risk (95% CI)	P-value
Study characteristics			
Mean length of follow-up	8	0.94 (0.87-1.00)	0.08
Sample size	8	1(0.99-1.00)	0.41
Year of publication	8	1(0.98-1.03)	0.91
Year of baseline	8	1(0.99-1.03)	0.43
Participant characteristics			
% Women	8	1.39 (0.74-2.61)	0.24
Mean age (10-year increase)	8	1.21 (0.99-1.48)	0.06
% Caucasian	8	1.05 (0.73-1.51)	0.76
Mean BMI (kg/m^2)	8	1.03 (0.96-1.10)	0.34
Mean LDL-C levels (10-mg/dl increase)	8	0.96 (0.92-1.00)	0.10
Mean glucose levels (10-mg/dl increase)	7	1.02 (0.90-1.16)	0.70
Mean systolic blood pressure levels (10-mmHG increase)	8	1.00 (0.99-1.02)	0.39
% Hypertensive	7	1.30 (0.89-1.89)	0.14
% Current smokers	8	0.48 (0.12-2.03)	0.26
% ASCVD	8	1.66 (0.75-3.65)	0.17

BMI = Body mass index
LDL-C = Low-density lipoprotein cholesterol
ASCVD = Atherosclerotic cardiovascular disease

IV. Supplemental references

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