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Still in the dark: effects of sex differences on statin-associated diabetes risk

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Statins reduce cardiovascular risk but modestly increase type 2 diabetes (T2D). Evidence is limited by underrepresentation of women and lack of sex-specific analyses. In an umbrella review and meta-analysis of 21 trials with sex-disaggregated data, statins increased T2D risk similarly in women (OR 1.28) and men (OR 1.24). However, absence of study-level data precluded assessment of statin-specific or absolute risks, highlighting the need for more research in this area.

Cardiovascular disease (CVD) is the leading cause of death globally, and statins are a cornerstone of guideline-directed therapy for both primary and secondary prevention. Their widespread use reflects strong evidence for reductions in low-density lipoprotein cholesterol (LDL-c) and cardiovascular events. However, statin use is also associated with a modest but statistically significant increase in incident type 2 diabetes (T2D), as demonstrated in a meta-analysis of statin trials by the Cholesterol Treatment Trialists' Collaboration (CTTC)[1].

CVD is the leading cause of death for both males and females in the United States, though age of onset differs by sex[2]. Despite this, the evidence base that informs statin guidelines is limited by the underrepresentation of females[3]. Clinically meaningful differences in cardiometabolic disease by sex, such as later CVD onset[4], differing distribution of some CVD subtypes[5], and greater diabetes-associated CVD risk in females[6] support routine reporting of treatment effects by sex, yet treatment recommendations are frequently extrapolated from randomized controlled trials (RCT) conducted predominantly or, in a few cases, entirely in males (e.g., the West of Scotland Coronary Prevention Study[7], the Multiple Risk Factor Intervention Trial [MRFIT][8], the Helsinki Heart Study[9], the Lipid Research Clinics Coronary Primary Prevention Trial[10], and the Veterans Affairs High-Density Lipoprootein Cholesterol Intervention Trial[11], among others). Among 60 lipid-lowering RCTs conducted from 1990 to 2018, women comprised only 28.5% of participants, and common eligibility restrictions included enrollment of only postmenopausal or surgically sterile women[12], gaps that are increasingly relevant as recent ACC/AHA cholesterol guidelines support earlier initiation of lipid-lowering therapy, including for some adults as young as 30 years[13]. Sex-stratified analyses were not routinely performed, although this has improved recently[14] (e.g., NIH NOT-OD-15-102[15]).

One domain in which questions remain is the role of sex in statin-associated diabetes risk. A meta-regression analysis of statin RCTs suggested that diabetes risk increased with the proportion of females enrolled in the trial[16]. Correspondingly, in a meta-analysis of observational studies, statin use was associated with more CVD events prevented than diabetes cases in both sexes, but the net benefit was smaller in females[17]. However, the CTTC analysis found that the relative effect of statin therapy on incident T2D risk was similar in females and males treated with low/moderate- or high-intensity statins[1]. Potential biologic explanations for statin-associated diabetes risk may also point to sources of heterogeneity: evidence from genome-wide association studies suggests shared genetic pathways between LDL-c lowering response to statins and diabetes risk[18], with 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)/mevalonate-related mechanisms postulated to affect insulin secretion[19] and insulin sensitivity[20]. This is accompanied by emerging experimental evidence suggesting that X-chromosome dosage and mitochondrial dysfunction may contribute to sex-specific differences in statin-associated dysglycemia. Whether these pathways translate into clinical differences by sex (or menopausal status) remains unclear. An important next step is to extend the work by evaluating sex-specific absolute risks and whether participant-specific characteristics (such as age and menopausal status) or statin-specific characteristics (such as treatment intensity) contribute to clinically meaningful differences in risk not captured by proportional effects alone.

Methods

To begin to address these questions, we sought to estimate sex-specific risks of statin-associated diabetes using data from RCTs of statins for primary and secondary prevention of CVD. We undertook an umbrella review of systematic reviews and meta-analyses (PROSPERO registration: CRD42023465344), including articles published from database inception to 12 March 2024, focusing specifically on placebo- or usual-care–controlled designs reporting incident diabetes. Trial-level data were extracted on diabetes incidence overall and, where available, by sex along with statin type, dose, follow-up duration, and participant characteristics. Risk of bias was assessed using the Risk of Bias instrument for Use in SysTematic reviews for Randomized Controlled Trials (ROBUST-RCT)[21]. Pooled odds ratios for incident diabetes were estimated using random-effects meta-analysis, with subgroup analyses to examine sex-specific effect modification.

Results

We identified 21 eligible studies (15 included in the CTTC analysis, 6 not included); however, none reported sex-stratified diabetes incidence. We contacted authors to request sex-disaggregated study-level data, and when responses were limited, engaged the CTTC. Using this approach, we were able to obtain data from all trials included in the CTTC analysis as well as study-level data for two additional trials[22,23]. Females comprised 27% of the analytic population ($n = 28{,}971$). Statin therapy was associated with a similar increase in type 2 diabetes risk in females (OR 1.28, 95% CI

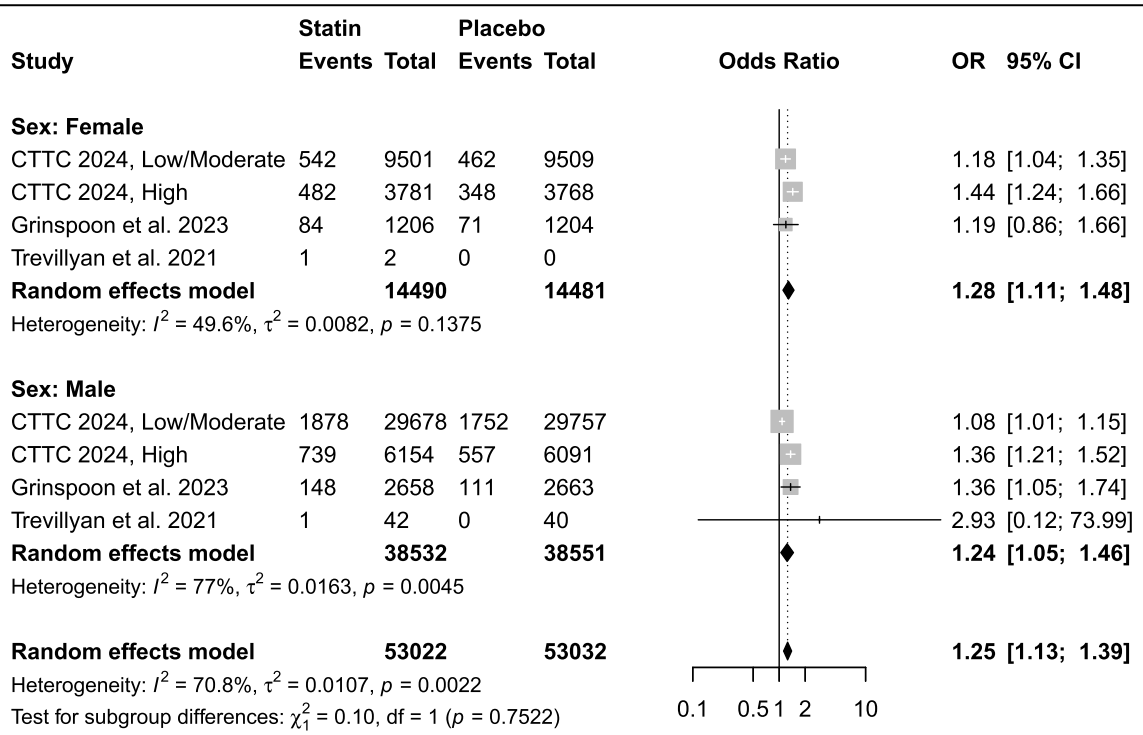

Fig. 1 | Odds ratios for incident diabetes associated with statin use. The figure shows pooled odds ratios for incident diabetes associated with statin use, including sex-specific subgroup analyses. CI confidence interval, CTTC Cholesterol Treatment Trialists' Collaboration, df degrees of freedom, OR odds ratio.

1.11–1.48) and males (OR 1.24, 95% CI 1.05–1.46), with an overall pooled OR of 1.25 (95% CI 1.13–1.39) (Fig. 1).

Discussion

In the current analysis, we found a similar ~25% greater odds of incident T2D with statin exposure in both females and males. The number of incident T2D cases in females (n = 1834) was adequate to support robust estimates of sex-stratified risks; however, the analysis may still have been underpowered to identify modest sex-specific differences[24]; thus, the extent to which female underrepresentation contributed to the null interaction remains uncertain. However, the absence of study- or participant-level sex-disaggregated data precluded our ability to assess whether pharmacological characteristics or treatment intensity might produce meaningful sex-specific differences in diabetes risk. It also impeded estimation of sex-specific absolute risks, which depend on baseline diabetes incidence and differ between females and males across age, risk strata, and menopausal status. Given the major benefits of statins for CVD risk reduction, it is unlikely that such findings would argue against statin use in patients with clear indications; rather, a more nuanced understanding of sex-specific and statin-specific risk profiles may inform the timing, choice, and intensity of therapy to support thoughtful shared decision-making in primary CVD prevention. In cardiometabolic health, next steps toward precision medicine may take the form of care tailored to characteristics that might meaningfully modify risk and treatment response. Based on what we know about the role of sex in life course risk of conditions such as CVD and T2D, additional work is needed to understand sex-specific risks and benefits, including sex-disaggregated estimates by statin and treatment intensity, and absolute risk estimates across relevant age and risk strata. Such reconsideration of the evidence is required to fully characterize the balance of risks and benefits of statin therapy for females and males across the life course, so that prescription and use of statins are based on sex-specific evidence.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available because they consist of extracted data from published studies included in this systematic review, but are available from the corresponding author on reasonable request.

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Author contributions

P.L.W. and A.J.P. contributed equally to this work; P.L.W. wrote the first draft of the manuscript, and A.J.P. performed the analyses. P.L.W., A.J.P., A.S.C., A.B., J.E.B.R., and J.G.R. designed the study. P.L.W., A.J.P., A.S.C., A.B., and M.O.W. conducted the systematic reviews. All authors contributed to manuscript revision and approved the final version.

Competing interests

J.G.R. is an Editorial Board Member of npj Women's Health. J.G.R. was not involved in the journal's review of, or decisions related to, this manuscript. The authors declare no other competing interests.

Additional information

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