

Association of Xanthelasma with Cardiovascular Risk: A Genuine Hazard or a Clinical Dilemma?

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Xanthelasma palpebrarum (XP)—the familiar yellowish, soft, cholesterol-rich plaques around the eyelids—is usually regarded as a benign dermatological or ophthalmological finding. Yet an apparently innocuous lesion may carry a more consequential message. For decades, clinicians have debated whether xanthelasma is simply a local manifestation of lipid deposition or a visible marker of systemic atherosclerotic disease. The question is deceptively simple: **does xanthelasma identify individuals at increased cardiovascular risk, or does its apparent association with cardiovascular disease merely reflect the dyslipidaemia and metabolic risk factors that commonly accompany it?**

The biological plausibility of an association is compelling. Xanthelasma represents accumulation of lipid-laden macrophages within the dermis and may be associated with abnormalities in cholesterol metabolism. A systematic review and meta-analysis of 15 case-control studies involving 854 patients with xanthelasma found higher concentrations of total cholesterol, LDL cholesterol and apolipoprotein B, together with relatively lower apolipoprotein A1 concentrations and greater carotid intima-media thickness than in controls ^[1]. These findings suggest that xanthelasma may coexist with an atherogenic lipid phenotype and subclinical atherosclerosis.

But association is not causation—and this distinction is particularly important for xanthelasma. The most frequently cited evidence comes from the Copenhagen City Heart Study, a large prospective population-based cohort of 12 745 individuals followed for up to 33 years. In that study, xanthelasma was associated with increased risks of myocardial infarction, ischaemic heart disease and total mortality, even after adjustment for conventional cardiovascular risk factors, including cholesterol and triglycerides. Xanthelasma was also associated with severe atherosclerosis ^[2]. These observations generated considerable interest because they suggested that the eyelid lesion might contain cardiovascular

information beyond a conventional lipid profile.

Yet subsequent evidence has complicated this attractive hypothesis. A systematic review and meta-analysis published in 2022 included six studies and 13 476 participants. When all studies were pooled, no statistically significant association was found between xanthelasma and ischaemic heart disease, stroke or overall cardiovascular disease. However, after exclusion of a study judged to have a serious risk of bias, the association with cardiovascular disease became significant, with an odds ratio of 1.65 (95% CI 1.05–2.61) ^[3]. The investigators therefore concluded that although a possible association exists, the available evidence remains limited and heterogeneous.

More recent evidence has again shifted the balance of the debate. A 2026 propensity-matched analysis using a large electronic-health-record database included 40 096 individuals—20 048 with xanthelasma and an equal number of controls. Patients with xanthelasma had higher rates of hyperlipidaemia and major adverse cardiovascular events; after adjustment, xanthelasma was associated with a hazard ratio of 1.26 (95% CI 1.22–1.31) for major adverse cardiovascular events ^[4]. These findings support the possibility that xanthelasma is more than a cosmetic marker. Nevertheless, the retrospective design means that residual confounding, ascertainment bias and differences in healthcare utilisation cannot be completely excluded.

An even more recent large propensity-matched analysis has reported substantially higher short- and long-term risks of myocardial infarction, stroke and transient ischaemic attack among patients with xanthelasma. At 10 years, myocardial infarction occurred in 3.13% of patients with xanthelasma compared with 1.73% of matched controls, while stroke occurred in 3.00% versus 1.53%, respectively ^[5]. Although these findings are striking, they should be interpreted in the context of the observational design and the limitations inherent to electronic-health-record studies. Conversely, a 2025 case-control study involving 203 patients with xanthelasma

and 2030 age- and sex-matched controls found no significant differences in dyslipidaemia, lipid concentrations, cardiovascular disease, hypertension or diabetes between the groups ^[6]. This negative study is important because it demonstrates that xanthelasma cannot reliably be regarded as an independent cardiovascular risk marker in every population.

So, where does this leave the clinician?

Perhaps the most defensible interpretation is that **xanthelasma should be regarded neither as a cardiovascular diagnosis nor as a meaningless cosmetic finding**. It is better viewed as a *clinical signal*. The lesion may identify a subgroup in whom conventional cardiovascular risk factors—particularly LDL cholesterol, non-HDL cholesterol, apolipoprotein B, diabetes, hypertension, obesity, smoking and family history—deserve careful assessment. However, the presence of xanthelasma alone should not be interpreted as evidence of established atherosclerotic cardiovascular disease.

This distinction matters. If xanthelasma is treated as a surrogate for cardiovascular disease, there is a risk of overdiagnosis and unnecessary investigation. Conversely, dismissing it entirely as cosmetic may represent a missed opportunity for preventive medicine. The clinician who notices xanthelasma has, in effect, encountered a readily visible biomarker whose incremental predictive value remains incompletely defined.

There is also an intriguing biological possibility. Xanthelasma may not simply reflect circulating cholesterol concentrations. Local macrophage biology, altered lipid transport, oxidised lipoproteins, inflammation and tissue-specific lipid handling could contribute to its development. This possibility might explain why some patients develop xanthelasma despite apparently normal conventional lipid profiles and why cardiovascular associations have not been consistently reproduced across populations ^[1,3,6]. The lesion may therefore represent a marker of *lipid susceptibility* rather than merely hypercholesterolaemia.

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The practical implication is consequently straightforward. **When xanthelasma is identified, the appropriate response is cardiovascular risk assessment—not cardiovascular alarm.** A lipid profile, blood-pressure measurement, assessment for diabetes, smoking status, body-weight assessment and evaluation of family history should be considered according to the patient's clinical context. Further investigations should be guided by established cardiovascular risk factors, symptoms and overall risk estimation rather than by the eyelid lesion alone.

The dilemma surrounding xanthelasma is therefore unlikely to be resolved by asking whether the lesion is a “genuine hazard” or a “false alarm”. It is probably both less dramatic and more useful than either description suggests. Xanthelasma is not equivalent to atherosclerosis, but accumulating observational evidence indicates that it may coexist with an adverse cardiovascular phenotype in at least some individuals [2–5]. The challenge is to distinguish the visible marker from the invisible risk.

Perhaps the most important lesson is that **the eyelid should not be regarded as a window that diagnoses cardiovascular disease, but it may be a window that prompts us to look more carefully.** Until prospective studies establish the incremental predictive value of xanthelasma beyond contemporary cardiovascular risk scores and lipid biomarkers, clinical prudence lies between complacency and overinterpretation. Xanthelasma should trigger assessment, not anxiety; prevention, not premature labelling. In cardiovascular medicine, that distinction may be the difference between recognising a useful clinical clue and creating a diagnostic dilemma.

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