

PCOS Linked to Increased All-Cause Mortality Risk in Women

Written by The Life Science Feed Editorial Team · Published 9 June 2026 · Edited by Mara Voss

Polycystic Ovary Syndrome (PCOS) affects a substantial proportion of women of reproductive age, presenting with a complex array of metabolic and reproductive disturbances. While its immediate impact on fertility and quality of life is well-recognised, the long-term implications for mortality risk have often been underappreciated in routine clinical practice. A comprehensive analysis of existing evidence now indicates that PCOS is independently associated with an increased risk of all-cause mortality, necessitating a re-evaluation of screening and management strategies.

KEY TAKEAWAYS

- ° The Pivot: PCOS is not solely a reproductive disorder but a systemic condition with significant long-term mortality implications.
- ° The Data: Women with PCOS exhibit a significantly elevated hazard ratio for all-cause mortality, with specific increases in cardiovascular and diabetes-related deaths.
- ° The Action: Clinicians should implement proactive screening for metabolic comorbidities and aggressive risk factor modification in all women diagnosed with PCOS.

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting approximately 6-10% of women of reproductive age.¹ It is characterised by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology.² Beyond its reproductive manifestations, PCOS is frequently associated with metabolic comorbidities including insulin resistance, type 2 diabetes mellitus, dyslipidaemia, and obesity.³ These metabolic disturbances are known risk factors for cardiovascular disease, raising concerns about long-term health outcomes in affected individuals. Despite the prevalence of PCOS and its associated metabolic profile, the direct impact on all-cause and cause-specific mortality has not always been consistently emphasised in clinical guidelines or patient management. This gap in understanding has led to a potential underestimation of the syndrome's systemic health burden.

The clinical presentation of PCOS is highly variable, ranging from mild menstrual irregularities to severe hyperandrogenic symptoms and significant metabolic derangements. The diagnostic criteria, primarily based on the Rotterdam criteria, require the presence of at least two of the three key features: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound, after exclusion of other aetiologies.² This heterogeneity in presentation can complicate epidemiological studies and clinical management, as the severity and specific constellation of symptoms may influence long-term health risks. Understanding the full spectrum of PCOS-related health consequences, including mortality, is crucial for developing comprehensive management strategies that extend beyond reproductive concerns.

What the evidence shows

Multiple cohort studies and meta-analyses have investigated the association between PCOS and mortality. A systematic review and meta-analysis pooling data from several large observational studies, including over 100,000 women, demonstrated a statistically significant increase in all-cause mortality among women with PCOS compared to age-matched controls.⁴ The pooled hazard ratio (HR) for all-cause mortality was 1.47 (95% CI, 1.28-1.69; P 4 This elevated risk was particularly pronounced for deaths attributed to cardiovascular disease, with a pooled HR of 1.82 (95% CI, 1.45-2.28; P 5 Deaths related to type 2 diabetes mellitus also showed a significant increase, with a pooled HR of 2.03 (95% CI, 1.55-2.66; P 5

The methodology of these meta-analyses typically involved a comprehensive search of electronic databases for observational studies reporting mortality outcomes in women with PCOS. Studies included were often population-based or hospital-based cohorts, with varying follow-up durations. The primary outcome measures were all-cause mortality and cause-specific mortality, particularly cardiovascular disease, diabetes, and cancer. Most analyses employed random-effects models to account for heterogeneity across studies, and sensitivity analyses often explored the impact of different diagnostic criteria for PCOS or adjustment for confounding factors. Patient populations in these studies were diverse, encompassing women from various geographical regions and ethnic backgrounds, reflecting the global prevalence of PCOS. However, the specific diagnostic criteria for PCOS and the methods for ascertainment of mortality varied, contributing to some heterogeneity in the pooled estimates.

The increased mortality risk appears to be mediated, at least in part, by the higher prevalence of metabolic syndrome components in women with PCOS. Insulin resistance, a hallmark of PCOS, contributes to the development of type 2 diabetes and dyslipidaemia.⁶ Chronic low-grade inflammation, also common in PCOS, further exacerbates atherosclerotic processes.⁷ Studies have shown that even after adjusting for body mass index (BMI), the association between PCOS and adverse metabolic profiles persists, suggesting independent contributions of the syndrome itself.⁸

The hyperandrogenism characteristic of PCOS may also play a direct role in metabolic dysfunction, potentially influencing adipose tissue distribution and insulin sensitivity. Elevated androgen levels are associated with increased visceral adiposity, which is a known risk factor for cardiovascular disease and type 2 diabetes.

While the evidence for increased cardiovascular and diabetes-related mortality is robust, the association with cancer mortality is less consistent across studies. Some analyses have reported a modest increase in endometrial cancer risk, likely due to unopposed oestrogen exposure resulting from chronic anovulation.⁹ However, the overall impact on cancer-specific mortality has not reached the same level of statistical significance or magnitude as cardiovascular and diabetes-related deaths in pooled analyses.⁴

Limitations of the current evidence base include the observational nature of most studies, which precludes definitive conclusions about causality. Confounding by unmeasured lifestyle factors or variations in diagnostic criteria for PCOS across different cohorts could influence the reported associations. Furthermore, the duration of follow-up in some studies may not be sufficient to capture the full spectrum of long-term mortality outcomes, particularly for conditions with prolonged latency periods. For instance, the development of certain cancers or the full impact of chronic metabolic stress on cardiovascular health may require decades to manifest. The lack of standardized diagnostic criteria for PCOS across studies also presents a significant limitation, potentially leading to misclassification bias and affecting the generalizability of findings. Future research should focus on prospective, long-term cohort studies with standardised diagnostic criteria and comprehensive adjustment for confounding variables to further refine these risk estimates. Intervention studies targeting metabolic risk factors in women with PCOS are also warranted to determine if aggressive management can mitigate the observed mortality risk.

CLINICAL IMPLICATIONS

The persistent underestimation of PCOS as a systemic metabolic disorder with significant mortality implications is a disservice to patients. For too long, the focus has been predominantly on reproductive concerns, often relegating metabolic screening to an afterthought. The data now unequivocally demonstrates that women with PCOS face a substantially higher risk of dying from cardiovascular disease and diabetes. This is not merely a statistical curiosity; it demands a fundamental shift in clinical practice. General practitioners and specialists alike must recognise that a PCOS diagnosis is a lifelong risk factor that requires proactive, aggressive management of metabolic comorbidities, not just fertility support.

Current guidelines, while acknowledging metabolic risks, often lack the urgency that these mortality data now impart. We need to move beyond annual glucose checks and consider more intensive screening for dyslipidaemia, hypertension, and early signs of cardiovascular disease. The pharmaceutical industry has largely focused on hormonal therapies for PCOS, but there is a clear unmet need for interventions that specifically target the long-term metabolic sequelae. Metformin, while beneficial for insulin resistance, is not a panacea for all cardiovascular risks. Perhaps the success of GLP-1 receptor agonists in type 2 diabetes and obesity could offer a new avenue, but their role in PCOS-specific mortality reduction needs dedicated investigation.

Patients with PCOS deserve to be fully informed of their long-term health risks. This is not about instilling fear, but empowering them with knowledge to engage in lifestyle modifications and adhere to medical therapies.

The narrative around PCOS must evolve from a 'women's issue' to a serious chronic condition requiring

comprehensive, multidisciplinary care. Failure to do so will continue to result in preventable morbidity and mortality, a consequence that is no longer justifiable given the accumulating evidence.

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