

# Sex-stratified dementia risk and population attributable burden across midlife and late life: toward a female-specific risk tool

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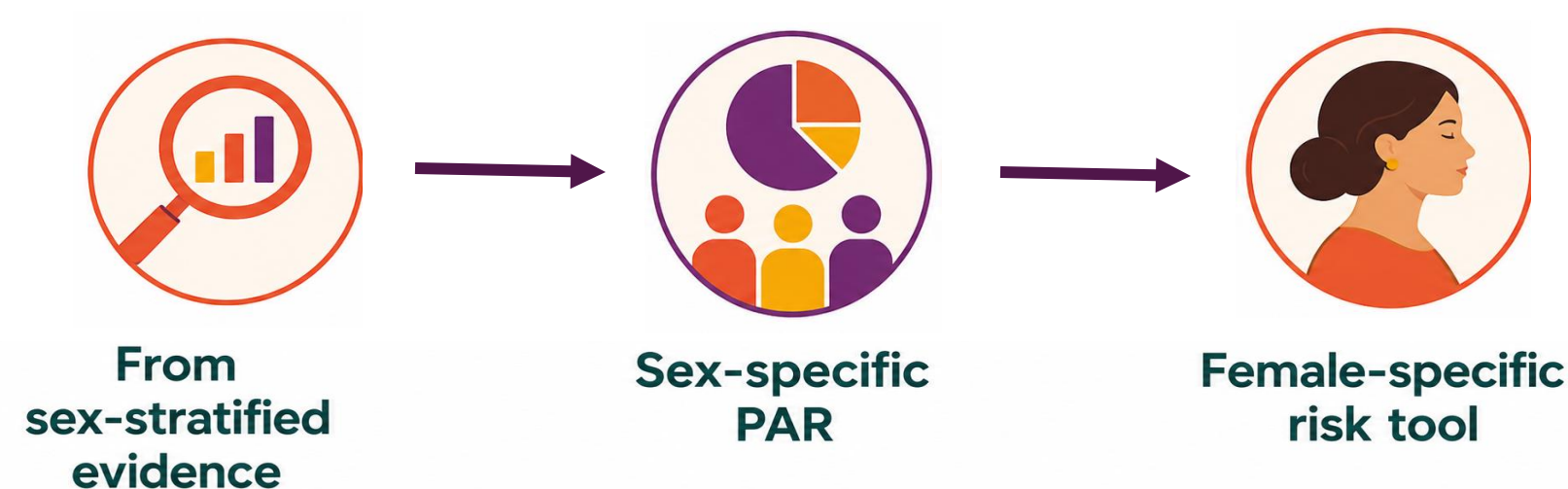
## BACKGROUND/OBJECTIVES

- Women account for ~two-thirds of dementia cases globally.<sup>1</sup>
- Up to 45% of dementia cases are linked to modifiable risk factors,<sup>2</sup> yet prevention estimates and PAFs are usually sex-aggregated.<sup>3</sup>
- Risk-factor prevalence and effects differ by sex.<sup>4, 5</sup>
- Existing risk tools, including CAIDE and ANU-ADRI, were developed in mixed-sex samples and perform differently by sex.<sup>6-8</sup>
- Current tools omit female-specific reproductive exposures, including reproductive span, hormone therapy, oophorectomy, and pregnancy complications.<sup>9, 10</sup>
- Objective:** Funded by Wellcome Leap CARE, this project aims to estimate sex differences in mid- and late-life dementia risk using sex-stratified RRs and sex-specific PAR. Findings will inform a female-specific dementia risk tool.

## METHODS

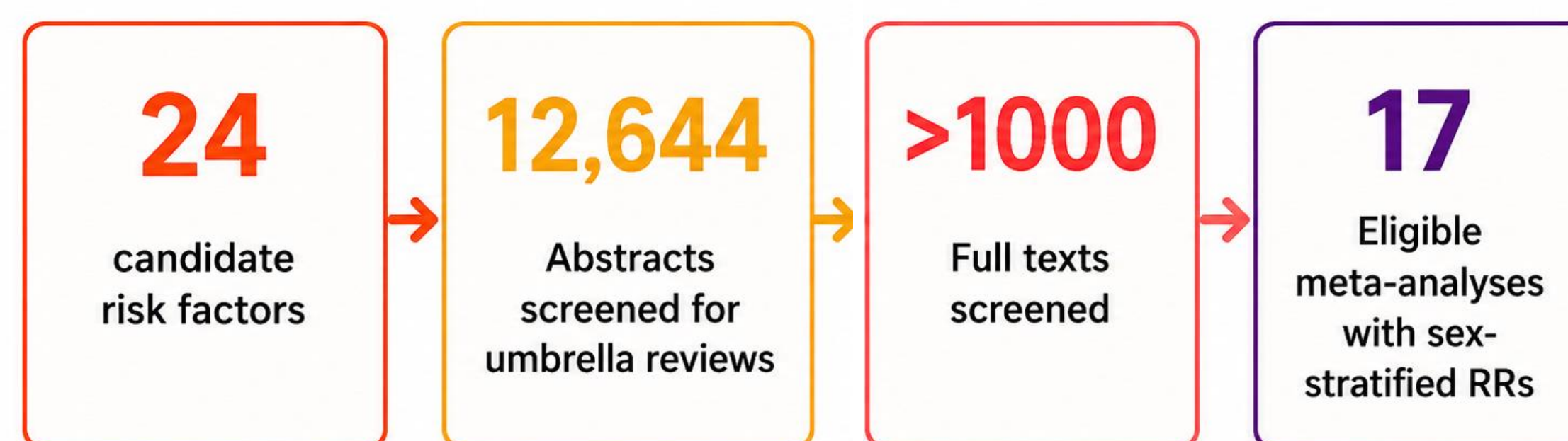
- Systematic reviews** of meta-analyses published in the past 10 years
- Focus on risk factors reported in the 2024 Lancet Commission report, plus understudied female-specific reproductive factors
- Lancet and other risk factors:** diabetes, smoking, physical inactivity, untreated vision loss, excessive alcohol consumption, obesity, traumatic brain injury, social isolation, diet, low education, untreated hearing loss, hypertension, air pollution, depression, high cholesterol, and sleep-related risks
- Female-specific factors:** reproductive period, menopause-related hormone therapy use and timing, hysterectomy, bilateral oophorectomy, number of pregnancies, pregnancy complications, hormonal contraceptive use.
- Objective:** identify **sex-stratified relative risks** for dementia. Where only sex-aggregated RRs exist, new systematic reviews or primary analyses are conducted
- Obtain **Sex-specific prevalence** data sourced from global datasets for future PAR estimation

## PROJECT SCOPE



## KEY PRELIMINARY RESULTS

First, we systematically searched the literature for published meta-analytic evidence:



Where published evidence was not available, we conducted new systematic reviews and meta-analyses, including for:

- Untreated vision loss
- Mid-life hypertension
- Depression
- Mid-life obesity
- Excessive alcohol consumption
- Traumatic brain injury (TBI)
- Mid-life high cholesterol

**44,225**

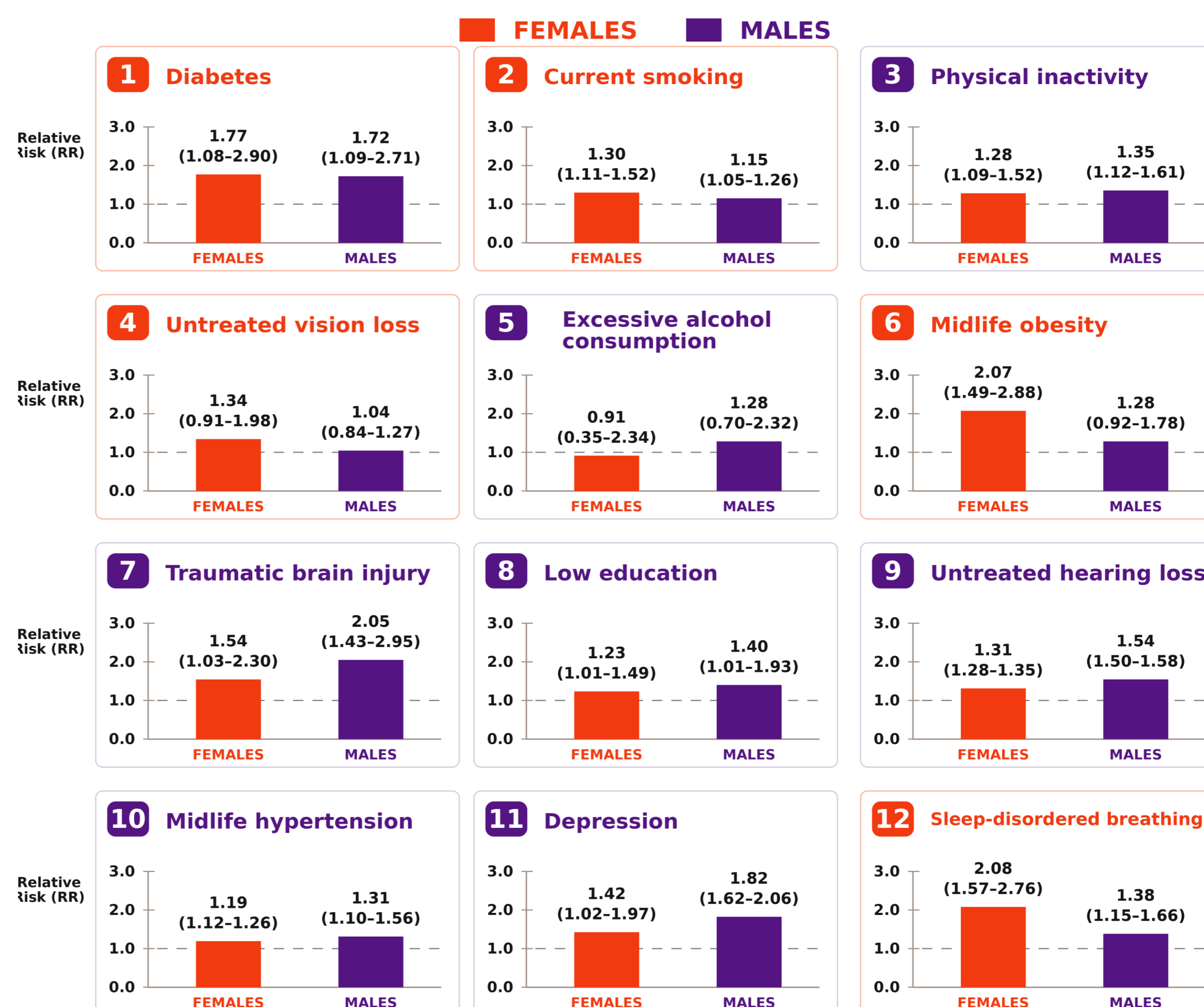
Abstracts screened for targeted systematic reviews where evidence was lacking

Our review of evidence for female-specific risk factors has been registered on PROSPERO and is underway.



There are notable sex differences in a range of modifiable risk factors.

Selected sex-stratified relative risks across modifiable dementia risk factors



## DISCUSSION

- Sex-aggregated metrics obscure women's true risk.** Because risk factors differ by sex, combined estimates can misrepresent women's actual risk and the prevention opportunities available to them.<sup>3, 4</sup>
- Our preliminary findings show both shared and sex-divergent factors.** Several established risks carried higher estimates in women (e.g., current smoking, mid-life obesity, sleep disordered breathing). Others were higher in males (e.g., excessive alcohol consumption, head injury, depression), and others showed equivalent risk across sexes. This reinforces that prevention priorities cannot be assumed equivalent across sexes.
- Female-specific reproductive factors remain outside mainstream frameworks.** Review-level evidence links menopause timing, surgical menopause, and hormone therapy to dementia risk, but this evidence is fragmented and, at times, contradictory limiting its translation into risk tools.<sup>9, 11, 12</sup>
- Quantifying sex-specific RRs, prevalences, and PAR is the necessary foundation** for identifying which factors offer the greatest prevention leverage in women and for personalised risk communication.<sup>5, 6</sup>
- Why this matters:** Moving beyond sex-aggregated prevention metrics will clarify women's attributable burden, sharpen sex-specific prevention priorities, and support a female-specific risk tool grounded in the best available global evidence.

## REFERENCES

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Professor Kaarin Anstey.