PERSPECTIVES IN HYPERTENSION

Sex differences in obesity and potential consequences for cardiovascular risk

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Hypertension in Women

Hypertension remains a key risk factor for cardiovascular disease (CVD) and premature death in women globally.[1] Around 600 million women worldwide are hypertensive, including hypertension during pregnancy, a leading contributor to maternal death.[1-3] However, hypertension in women (and in men) is underdiagnosed and undertreated, with control rates as low as 23% among women with hypertension.[1,3]

Thus, better prevention, detection, and treatment of hypertension in women are critical healthcare challenges. Established risk factors for hypertension, including unhealthy diet and lifestyle, obesity, and aging, are common among both men and women and are well-recognized in practice guidelines for clinical care.

However, women or female-specific factors remain understudied in basic, clinical, and population research. These risk factors are not only related to menarche, reproduction, menopause, and (pharmacological use of) sex hormones, but also to the (strength of the) association between established risk factors such as obesity and hypertension and CVD, with often a stronger association between risk factor burden and adverse effects in women than in men.[1,4,5] Furthermore, recent sex-specific analyses have suggested that blood pressure increases more rapidly with aging among premenopausal women than among age-matched men. In addition, blood pressure treatment thresholds and efficacy of interventions to lower blood pressure and cardiovascular disease risk may differ between sexes (Box 1).[1,4,5] Recent papers relevant to this topic are discussed below.[6,7]

Box 1. Hypertension in women[1]

- The rise in blood pressure during the life course of women is steeper than in men
- Women-specific risk factors for hypertension and CVD include gynecological disorders, complicated pregnancies, and early menopause
- Evidence indicates that hypertension control declines with aging in women
- The association of blood pressure with poor outcomes seems stronger in women
- Women and gender-specific aspects of hypertension treatment are understudied

Increasing Obesity Among Women

The NCD Risk Factor Collaboration (NCD-RisC), a network of health scientists around the world who collaborate to collect and analyze data on major risk factors for non-communicable diseases, published a paper on worldwide trends in underweight and obesity from 1990 to 2022, with data from 3663 population-representative studies including 222 million children, adolescents, and adults residing in 200 countries and territories.[6]

Pooled data from population-based studies with height and weight measurements in samples of the general population were analyzed using a Bayesian hierarchical meta-regression model. The primary outcome was the individual and combined prevalence of underweight (adults; age ≥20 years)

or thinness (school-aged children and adolescents; age 5–19 years) and obesity. Underweight was defined as a body mass index (BMI) of less than 18.5 kg/m2 and thinness as a BMI less than two SD below the median of the WHO growth reference. Obesity was defined as a BMI of 30 kg/m2 or higher for adults and a BMI of more than two SD above the median of the WHO growth reference for children and adolescents. The data and details of the statistical methods are available at https://ncdrisc.org/.

The main conclusion from this analysis, which covers more than 99% of the world's population, was that obesity has starkly increased in recent years, and that this rise affects children and young adults increasingly. The global age-standardised prevalence of obesity increased from 8.8% (95% credible interval, 8.5–9.1) in 1990 to 18.5% (17.9–19.1) in 2022 in adult women and from 4.8% (4.6–5.0) to 14.0% (13.4–14.6) in adult men. The number of women and men with obesity in 2022 was 504 million (489–520) and 374 million (358–391), respectively, which was an increase of 377 million (360–393) and 307 million (290–324), respectively, from 1990. The countries with the largest absolute numbers of adults with obesity in 2022 were the USA, China, and India.

Over the same period, the age-standardized prevalence of obesity increased in girls in 186 countries (93%) and in boys in 195 countries (98%). In most countries, obesity in children more than doubled. The global age-standardised prevalence of obesity in school-aged children and adolescents increased from 1.7% (1.5–2.0) in 1990 to 6.9% (6.3–7.6) in 2022 in girls and from 2.1% (1.9–2.3) to 9.3% (8.5–10.2) in boys. The number of girls and boys with obesity in 2022 was 65.1 million (59.4–71.7) and 94.2 million (85.3–103.0), respectively, an increase of 51.2 million (45.2–57.8) and 76.7 million (67.6–85.7), respectively, from 1990. In almost all countries, there was an increase in obesity and a decline in underweight or thinness among school-aged children, adolescents, and adults. Visualisations per country can be viewed on the NCD-RisC website.

Obesity, Hypertension, and Cardiovascular Disease Risk

A different paper by this group concerned the rise in blood pressure during this period.[3] In that paper, hypertension was defined as having systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or taking medication for hypertension. Controlled hypertension was defined as taking medication for hypertension and having systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg. These analyses were restricted to men and women aged 30–79 years.

The data indicated that the number of people with hypertension doubled from 1990 to 2019, from 331 (95% credible interval, 306–359) million women and 317 (292–344) million men in 1990 to 626 (584–668) million women and 652 (604–698) million men in 2019, despite the stable global age-standardised prevalence. Globally, 47% (43–51) of women and 38% (35–41) of men were treated. Control rates among people with hypertension in 2019 were 23% (20–27) for women and 18% (16–21) for men.

In 2019, the global age-standardised prevalence of hypertension in adults aged 30–79 years was 32% (30–34) in women and 34% (32–37) in men, similar to 1990 levels of 32% (30–35) in women and 32% (30–35) in men. The stable global prevalence was a net effect of a decreased prevalence in high-income countries and an increase in low-income and middle-income countries.

However, it is important to note that there are data indicating that a threshold of 140/90, as used in most parts of the world, or even 130/80, might be too high for women, as recent studies show that these thresholds for treatment might not adequately reduce cardiovascular risk in women.[4,5,7,8] A recent Women's Health Initiative analysis suggested that optimal systolic blood pressure levels in women might be around 100 at age 65.[7] In addition, different pathways seem to link obesity with hypertension and cardiovascular disease more detrimentally in women compared to men. This includes perturbations in the regulation of sex hormones, insulin resistance, sodium sensitivity, inflammatory responses, sympathetic nervous system activation, endothelial and neuroendocrine dysfunction, skeletal muscle characteristics, and gynecological disorders.[1,9-13]

Obesity, sodium sensitivity, and hypertension are strongly associated in women, and the prevalence of uncontrolled hypertension is higher in obese than in non-obese women.[1,9] Higher lipoprotein lipase activity, greater lipolysis in response to lipolytic stimuli, and greater suppression of lipolysis by insulin in the fed state create stronger

drivers of obesity in females compared to males.[10] Furthermore, the neuroendocrine hormone leptin and the renin-angiotensin system may contribute to obesity-associated hypertension via sex-specific mechanisms.[1,9-13]

Leptin is thought to have a key role in obesity in women, regulating food intake, metabolism, and fat distribution. Leptin may affect blood pressure independent of obesity through sympathetic activation.[1,9,11] Plasma leptin levels are higher in women than in men at any given measure of obesity, consistent with a state of relative leptin resistance.[1,9,11] Progesterone is thought to promote leptin-mediated endothelial dysfunction in obese premenopausal women through aldosterone and endothelial mineralocorticoid receptors,[9] and leptin has also been implied in the high prevalence of obesity in women with gynecological disorders.[13,14]

Conclusion

In summary, obesity in women may affect hypertension risk and cardiovascular disease through sex-dimorphic pathways. Therefore, the consequences for hypertension and cardiovascular risk of the large increase in the global prevalence of obesity among women recently reported need to be critically assessed, taking sex-specific mechanisms in the development of hypertension and cardiovascular disease into account.

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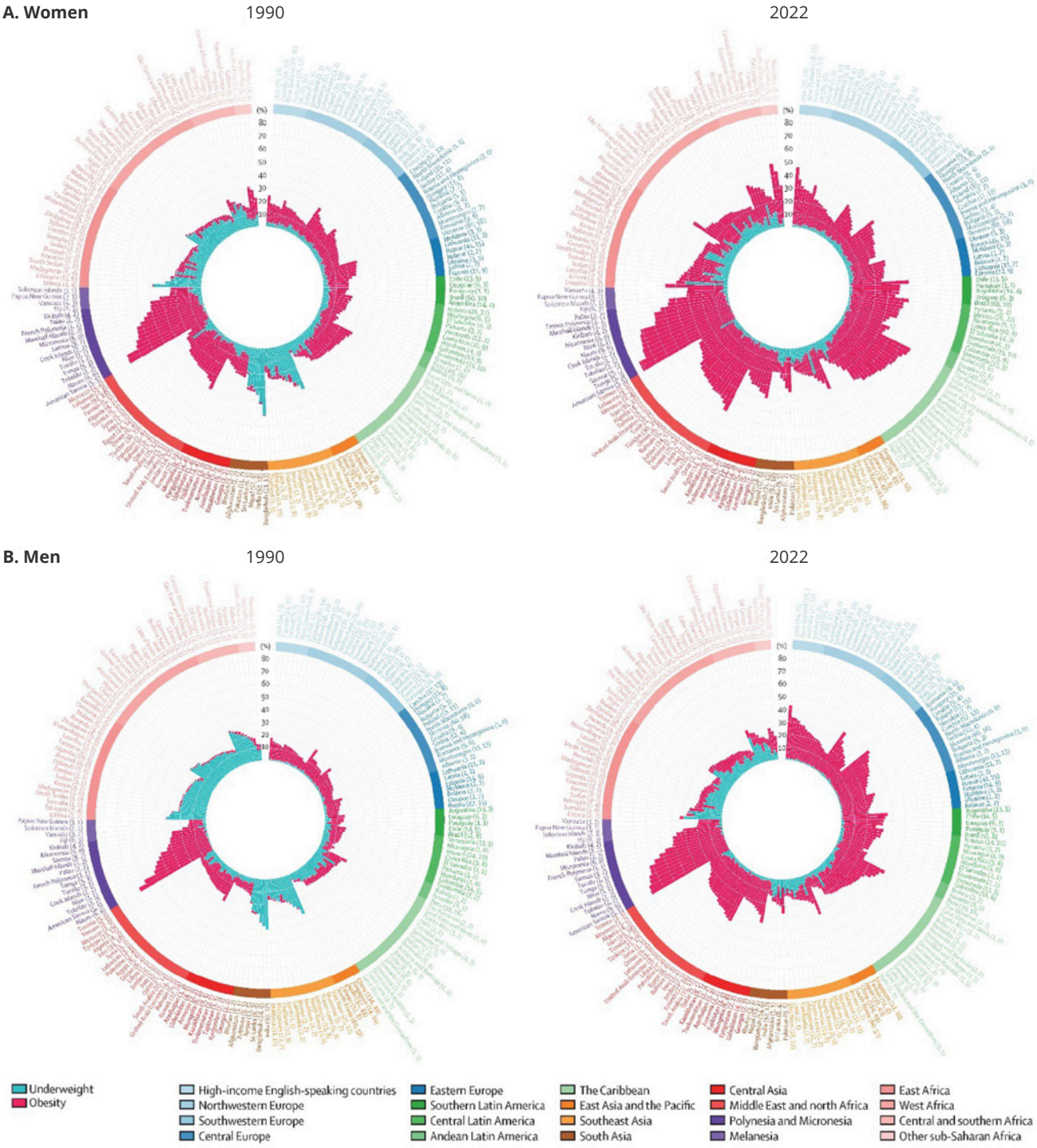
Figure 1 Increase in age-standardised combined prevalence of underweight and obesity between 1990 and 2022, by country, for adults (age ≥20 years), indicating a greater increase in women.[6] A. Women, B. Men. The circular bar plots show the burden of underweight and obesity in 1990 and 2022. The lengths of the bars show the age-standardised prevalence of underweight (blue) and obesity (red), and their sum shows the age-standardised combined prevalence, indicating a higher prevalence of obesity in women. Country names are coloured by region. The numbers in brackets after each country's name show the total number of data sources and the number of nationally representative data sources, respectively. The maps show the change in combined prevalence of underweight and obesity from 1990 to 2022, and its level in 2022. NCD Risk Factor Collaboration.[6] Published with permission of the NCD Risk Factor Collaboration and Elsevier Publishers under CC-BY license.



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