The ‘obesity paradox’ in cardiovascular diseases: age matters!

Marouane Boukhris and Victor Aboyans

1Department of Cardiology, Dupuytren-2 University Hospital, Limoges, France; and 2EpiMaCT, INSERM 1094 & IRD 270, Limoges University, Limoges, France

This editorial refers to ‘Age-dependent associations of body mass index with myocardial infarction, heart failure, and mortality in over 9 million Koreans’, by H.-J. Lee et al., https://doi.org/10.1093/eurjpc/zwac094.

One of the most challenging health issues in this century is the booming rates of obesity. Since 1980, the prevalence of overweight and obesity doubled in both genders worldwide, including in developing countries. Numerous health complications are related to obesity, making it a modifiable risk factor for a variety of diseases, including Type 2 diabetes, hypertension, and cardiovascular diseases (CVDs). Furthermore, obesity, either alone or associated with metabolic syndrome, is associated with an increased risk of all-cause death.3

Nonetheless, several reports have demonstrated that overweight or obesity appears to exert a protective effect in patients with diagnosed CVD, the so-called obesity paradox. Ample evidence has confirmed the presence of this paradox in large cohorts, where overweight and obese patients display a better prognosis when suffering from different CVDs, e.g. myocardial infarction (MI), and heart failure (HF).3

However, a number of confounding factors can bias the relationship between obesity and CVD prognosis, including the type of adiposity, CVD severity/duration, comorbidities, gender, and age.3 Indeed, obese patients with CVD are often younger at the time of CVD onset and may receive more intensive care. In general, the association between body mass index (BMI) and mortality is ‘U-shaped’, with the highest mortality in the case of underweight or extreme obesity. However, factors contributing to weight gain and loss may differ in different periods of life, and mortality causes also differ in different ages. It is, therefore, legitimate to question whether the typical U-shaped association between BMI and mortality is constant in all age groups. In this issue, Lee et al.4 addressed this question through an in-depth analysis of the Korean National Health Insurance Service database. The investigators assessed the relationship between BMI, age, and the occurrence of MI, HF, and all-cause death in the long term in more than 9 million Koreans without prior CVD.4 All individuals in this database were subdivided into six BMI categories according to World Health Organization guidelines on Asians: severely underweight (<17 kg/m²), mildly underweight (17–18.4 kg/m²), optimal normal weight (18.5–22.9 kg/m²), high normal weight (23–24.9 kg/m²), pre-obese (25–29.9 kg/m²), and obese (≥30 kg/m²), stratified in three age bands: young (20–39 years), middle-aged (40–64 years), and elderly (≥65 years).4

The main result of their analysis was that all associations between BMI and the investigated outcomes were found to be significantly modified by age (P-for-interaction <0.001).4 Overall, obesity appeared as a risk factor with incident events in the youth (20–39 years), while it seemed increasingly ‘protective’ over age, because in the elderly (≥65 years), only underweight individuals were found to be at the highest risk. Interestingly, ‘pre-obesity’ (i.e. overweight) was associated with the greatest survival benefit. In young individuals, the higher the BMI the higher the incidence of MI, while this relationship became U-shaped in middle-aged individuals, and inversely proportional/plateauing in the elderly.4

Being overweight was associated with an increased risk of HF in all ages, and the U-shaped association between BMI and incident HF was observed in the three age bands. However, the impact of obesity was found to be stronger in young individuals, while the impact of underweight was stronger in middle-aged and elderly individuals.4

The literature is controversial regarding the precise role of ageing on the obesity paradox for CVD. Impaired, unchanged, or improved outcomes are reported for overweight or obesity and the prognosis of various CVDs with ageing (Table 1).4–11

Obesity in the elderly appears to be more complex in terms of its associated risk of mortality. Compared with individuals younger than 65 years of age, the elderly (>65) generally possess a much lower BMI and more comorbidities for CVD, therefore altering the obesity paradox.3

Although moderate obesity in later life may improve survival and alleviate frailty and cachexia, this obesity paradox is suggested to be related to possible confounding factors such as weight loss related to other harmful factors such as smoking and disease-induced unintentional weight loss.3 Notably, the findings by Lee et al.4 were independent of sex, smoking, physical activity, and comorbidities.
Table 1  Studies investigating the impact of age on the relationship between body mass index and cardiovascular disease

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>N</th>
<th>Population</th>
<th>Country/area</th>
<th>Follow-up</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens et al. (1998)</td>
<td>324 135</td>
<td>Non-smoking American whites w/o prior CVD or cancer</td>
<td>USA</td>
<td>12 years</td>
<td>High BMI was associated with increased mortality in the younger generations and low BMI was associated with increased mortality in the very elderly (≥85 years)</td>
</tr>
<tr>
<td>Jee et al. (2006)</td>
<td>1 213 829</td>
<td>Individuals w/o prior CVD, cancer, liver disease, diabetes, or respiratory disease</td>
<td>Korea</td>
<td>&gt;5 years</td>
<td>J-shaped association between BMI and all-cause mortality; the lowest risk within BMI 23.0–24.9 kg/m² range. Age attenuated the association of high BMI with all-cause death</td>
</tr>
<tr>
<td>Clark et al. (2014)</td>
<td>2 466</td>
<td>Black Americans and Africans ≥70 years</td>
<td>USA and Nigeria</td>
<td>10 years</td>
<td>After 70 years, survival was similar among BMI classes</td>
</tr>
<tr>
<td>Fukuoka et al. (2019)</td>
<td>1641</td>
<td>MI patients with primary percutaneous coronary intervention</td>
<td>Japan</td>
<td>620 days (median)</td>
<td>In patients &lt;70 years, high BMI was associated with higher all-cause mortality. In contrast, patients ≥70 years with low BMI had a significantly higher all-cause mortality</td>
</tr>
<tr>
<td>Millet et al. (2018)</td>
<td>471 998</td>
<td>Individuals w/o prior CVD</td>
<td>UK</td>
<td>7 years (mean)</td>
<td>High BMI was associated with an increased risk for MI, but the association weakened with older age</td>
</tr>
<tr>
<td>Banack et al. (2020)</td>
<td>68 132</td>
<td>Post-menopausal women</td>
<td>USA</td>
<td>12 years</td>
<td>The relative mortality risk associated with high BMI decreased with increasing age</td>
</tr>
<tr>
<td>Tromp et al. (2021)</td>
<td>24 675</td>
<td>Individuals w/o history of HF</td>
<td>Multinational multi-ethnic</td>
<td>12.7 (median)</td>
<td>Age did not modify the effect of high BMI on HF incidence</td>
</tr>
<tr>
<td>Lee et al. (2022)</td>
<td>9 278 433</td>
<td>Individuals w/o prior CVD</td>
<td>Korea</td>
<td>8.3 years (median)</td>
<td>Proportional increase in MI risk according to BMI in young individuals; this association became U-shaped in middle-aged subjects and inversely proportional/plateauing in the elderly</td>
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<td></td>
<td>U-shaped relationship between BMI and incident HF, but the impact of obesity was stronger in young subjects, while the impact of underweight was stronger in middle-aged/elderly subjects</td>
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<td>Lower BMI was associated with higher all-cause mortality in all ages, although this association was attenuated at young age</td>
</tr>
</tbody>
</table>

BMI, body mass index; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; w/o, without.
The influence of age on the obesity paradox can also be affected by the follow-up duration. In a meta-analysis, the obesity paradox was evident with a short follow-up in severely obese patients, while such association was lost after 5 years of follow-up. Likewise, patients with ischaemic heart disease with moderate or severe obesity exhibited a higher mortality during the long-term follow-up. In their analysis, Lee et al. assessed the outcome beyond the first year of follow-up, so as to avoid the possibility that some patients with poor conditions and low survival bias the data.

The influence of age on the obesity paradox requires close attention because of ethnicity variations. Asians have increased cardiovascular risk at lower BMI cut-offs than Caucasians and have higher abdominal and body fat percentages at the same BMI. This could make it difficult to generalize these findings to European, North American, and even African populations. For instance, in a study involving older African Americans and Yoruba Nigerians, the overall 10-year survival rates were remarkably similar in different BMI groups.

The authors performed some additional analyses, excluding secondary causes of sarcopenia, as sensitivity analysis. Although BMI represents the most practical index to assess obesity, it is not able to discriminate between fat mass, lean mass, and adiposity subtypes. With ageing, important changes in body composition occur with significant variations in the fat/lean mass ratio. Indices such as waist circumference, waist-to-hip ratio, and percent body fat might be better tools to reflect body fatness and predict cardiovascular risk through different age groups. In the Lee et al. study, abdominal obesity was related to higher cardiovascular events and all-cause mortality rates for all ages, except for obese subjects aged ≥70 years. In addition, there was a trend for stronger protective effects of obesity on all-cause mortality in subjects with abdominal obesity in the middle-aged and elderly groups. These findings suggest the attenuation of the harmful effect of visceral adiposity in older people.

While weight loss is beneficial for cardiac health, as well as for other comorbidities, definitive clinical guidelines are still lacking for the optimal body composition, especially in the elderly. In the light of their results, Lee et al. recommend weight loss only to younger overweight individuals. Intentional weight loss in the obese elderly is generally considered safe and beneficial for several obesity-related diseases. Weight loss diets are recommended, in combination with exercise programmes, to preserve muscle mass and prevent loss of muscle as well as fat. This is particularly important for elderly patients to counteract sarcopenia.

Finally, this study has been performed in a country with one of the highest life expectancies worldwide (>82 years), so that the limit of 65 to define elderly might be discussable from this standpoint, and future studies are necessary to fine-tune the association of obesity and CVD in the elderly vs. the very elderly (e.g. >80 years).

While Lee et al. should be commended for their major contribution to address the complex relationship between obesity and CVD, future studies including multi-ethnic populations are still necessary to investigate the impact of BMI change on CV outcome in different age groups and guide clinicians for adapted recommendation according to the age of their patients.

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**References**


