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Association of body mass index with mortality in cardiovascular disease: New insights into the obesity paradox from multiple perspectives☆

Jonathan Y. Xia, MD[a], Donald M. Lloyd-Jones, MD, ScM[c], Sadiya S. Khan, MD, MS, FACC[b,c,*]

[a] Department of Medicine, Northwestern University Feinberg School of Medicine, United States
[b] Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, 680N. Lake Shore Drive, 14-002, Chicago, IL 60611, United States
[c] Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, United States

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ABSTRACT

Over the past 4 decades, prevalence of obesity has increased rapidly at both the national and global level and presents a major public health challenge. Obesity is associated with increased risk of morbidity from cardiovascular diseases. Data suggesting that the presence of obesity may be protective in individuals with clinically manifest cardiovascular disease have led to discussion of an "obesity paradox", stirring controversy and leading to unclear messaging regarding the true health risks of excess weight. This review explores the relationship between obesity and fatal and non-fatal outcomes in patients with prevalent cardiovascular disease and offers novel insights into the obesity paradox.

Introduction

Obesity is a major risk factor for cardiovascular disease (CVD) and numerous comorbidities, such as type 2 diabetes, dyslipidemia, and hypertension [1]. Obesity is also associated with increased burden of non-cardiovascular comorbidities, including osteoarthritis, sleep apnea, pulmonary disease, and malignancy [2]. The burden of obesity in terms of healthcare costs continues to increase dramatically with direct and indirect medical care costs attributed to obesity exceeding $147 billion in 2008 [3]. Large-scale, long-term studies have consistently demonstrated increased risk of CVD morbidity and mortality in overweight and obese individuals [4]. However, in recent years controversy regarding the health implications of overweight and obesity has grown in patients with prevalent CVD, given findings of similar or lower all-cause mortality compared with normal weight patients with CVD [5].

The rising prevalence of obesity to epidemic levels and the increasing health care costs secondary to obesity and obesity-related diseases led to the initial impetus to establish guidelines to address the identification, evaluation, and treatment of overweight and obesity. In 1995, the National Institutes of Health convened the first expert panel to develop clinical practice guidelines for care providers. Based on the evidence examined by the panel, body mass index (BMI), which is calculated as body weight in kilograms divided by height in meters squared, was chosen to assess weight categories due to its ease and practicality [6]. BMI categories were defined as normal weight (BMI of 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (30 kg/m^2) for individuals over 18 years of age. In youth, overweight is defined as a BMI at or above the 85th percentile and below the 95th percentile based on population standards from 2000. Obesity is defined as BMI at or above the 95th percentile of youths of the same age and gender [7]. In 2013, the American Heart Association (AHA), American College of Cardiology (ACC), and the Obesity Society compiled updated guidelines for management of obesity recommending weight loss in individuals who are obese or overweight with at least one risk factor for CVD or obesity-related comorbidity [8].

This manuscript will review secular trends in overweight and obesity in the general population and describe associations of BMI with fatal and non-fatal outcomes. We will provide novel insights into the obesity paradox and examine potential confounders that may be relevant in the relationship of BMI with CVD and mortality. Finally, we will describe areas of equipoise where further research is urgently needed to provide clinicians with guidance on weight loss recommendations in patients with cardiovascular disease.

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* Corresponding author at: Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, United States.
E-mail address: s-khan-1@northwestern.edu (S.S. Khan).

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Secular trends in overweight and obesity in youth and adults

Since 1980, the prevalence of obesity has nearly doubled in more than 70 countries with estimates that a total of 107.7 million children and 603.7 million adults were obese in 2015 [9]. In the United States, approximately 39.6% of US adults and 18.5% of youths were obese according to data from the National Health and Nutrition Examinations Survey 2015–2016 [10]. Further, 7.7% of adults and 5.6% of youths had severe obesity. According to the National Longitudinal Study of Adolescent Health, adolescents who were obese had a 16-fold increased risk of having severe obesity as adults, and 70.5% of adolescents with severe obesity maintained this weight status into adulthood [11].

Obesity, cardiovascular health, and cardiovascular disease across the life course

There are substantial adverse cardiovascular effects of overweight and obesity. Obesity is associated with the development of cardiovascular risk factors such as hyperlipidemia, hypertension, atherosclerosis, type 2 diabetes and metabolic syndrome as well as increased lifetime risk of incident CVD (coronary heart disease, stroke, atrial fibrillation, and heart failure) [4,6]. As a result, the AHA identified maintenance of a normal BMI as 1 of the 7 key components of ideal cardiovascular health (CVH) in 2010. The full spectrum of CVH incorporates ideal presence and levels of health behavior (smoking status, physical activity, diet, in addition to BMI) and health factor (cholesterol, blood pressure, and fasting glucose) metrics. Unfortunately, CVH typically declines from birth through adulthood, and only 63.1% of youth and only 29.6% of adults met these criteria in 2013–2014 [1].

Multiple analyses have demonstrated adverse association of BMI with CVH metrics and CVD outcomes in children and adolescents. In an analysis of 8579 children and young adults from NHANES between 1999 and 2012, higher BMI was associated with higher systolic and diastolic blood pressures, dyslipidemia, and insulin resistance [12]. In another study examining longitudinal data from 2.3 million adolescents (ages 16–19 years), higher cardiovascular mortality rates were observed in adulthood (Hazard Ratio [HR] of 3.5 [95% confidence interval [CI] 2.9, 4.1]) in obese youth compared with youth with BMI in the 5th to 24th percentile [11]. Since the prevalence of obesity has steadily increased for adolescents over the past decade, this increased duration and burden of obesity will adversely affect individual-and population-level cardiovascular health across their life course.

BMI has been demonstrated to be tightly associated with adverse cardiovascular structure and function in young adulthood. In a prospective analysis from the Coronary Artery Risk Development in Young Adults (CARDIA) study, greater duration of obesity from young adulthood to middle age was associated with presence of and progression of subclinical atherosclerosis as well as greater left ventricular mass, left ventricular end diastolic volume, and left atrial dimension [13,14]. Higher BMI at age 17 years in healthy participants from the Avon Longitudinal Study of Parents and Children was causally associated with higher blood pressure and left ventricular mass index, supporting the role for earlier intervention in young adulthood to prevent adverse CV outcomes across the lifespan [15].

Long-term follow-up data have also examined the adverse effects of BMI on cardiovascular outcomes in middle age to older adults. A recent study of participants from 7 prospective cohorts using mendelian randomization demonstrated that genetic variants associated with BMI conferred an increased risk of incident atrial fibrillation suggesting a causal link between excess weight and atrial fibrillation [16]. Data from the Cardiovascular Lifetime Risk Pooling Project from 10 prospective cohort studies, including 190,672 person-examinations and over 3.2 million person-years of follow-up demonstrated that obesity is associated with shorter longevity and significantly increased risk of cardiovascular morbidity, resulting in a greater proportion of life lived with CVD morbidity compared with normal BMI [4]. In aggregate, these data spanning from childhood to older adulthood support the importance of preventing or delaying the onset of obesity to lower the risk and burden of CVD resulting in a healthier, longer life.

The obesity paradox in patients with cardiovascular disease

Multiple studies have demonstrated that overweight and obese patients may have a more favorable prognosis when compared to their counterparts with normal BMI after onset of clinical CVD. These controversial findings have been termed the “obesity paradox”. Since the first report more than 20 years ago, publications of research findings investigating the obesity paradox have progressively increased over the years with 895 manuscripts identified in Scopus with “obesity paradox” in the title or abstract (Fig. 1). Here, we will review the available literature on the presence of the obesity paradox in specific CVD (coronary artery disease and heart failure) and non-CVD subgroups.

Coronary artery disease

More than twenty years ago, Ellis *et al* reported lower rates of in-hospital mortality in patients with coronary artery disease (CAD) with a BMI between 26 and 34 kg/m^2 compared to patients with a BMI less than 25 kg/m^2 following percutaneous coronary intervention (PCI) in a single center study [17]. Among 9633 patients with CAD undergoing PCI between 1994 and 1999, overweight and obesity status was associated with lower in-hospital complications and 1-year mortality [18]. In a study from the British Cardiovascular Intervention Society Registry that included 345,192 patients from 2005 to 2013, patients with an elevated BMI ($\geq$25 kg/m^2) had significantly lower mortality in short (30-day), medium (1-year) and long-term (5-year) follow-up when compared to patients with normal BMI (18.5–24.9 kg/m^2) at the time of PCI [19]. In a large systematic review that included 40 studies and 250,152 patients with coronary artery disease, obese patients had no increased risk for total mortality (0.93 [0.85–1.03]) or cardiovascular mortality (0.97 [0.82–1.15]) when compared with normal BMI. Among patients with acute coronary syndromes, overweight, obese, and severely obese participants had lower mortality compared with normal BMI (RR ranging from 0.60 to 0.70) [20].

Heart failure with preserved and reduced ejection fraction

An apparent obesity paradox has also been observed in patients with heart failure (HF), similar to patients with CAD. One of the earliest studies to demonstrate this was a retrospective analysis in over 7000 patients with stable heart failure (HF) enrolled in the Digitalis Investigation Group trial. Over the mean follow-up of 37 months, overweight and obese patients with HF had lower risks of all-cause mortality and death due to worsening HF compared to normal weight patients [21]. This study also showed that underweight patients were at higher risk of death, highlighting the morbidity of chronic disease states associated with wasting. Analyses in over 100,000 patients enrolled in the Acute Decompensated Heart Failure National Registry found that higher BMI ($>$25.0 kg/m^2) was associated with lower risk of in-hospital mortality for HF patients during acute HF hospitalizations compared with normal BMI, but the highest rate of in-hospital mortality was in underweight patients (BMI $<$ 18.5 kg/m^2) [22]. A meta-analysis of nine observational studies of HF patients also found that obesity was associated with lower all-cause and CV mortality rates [23].

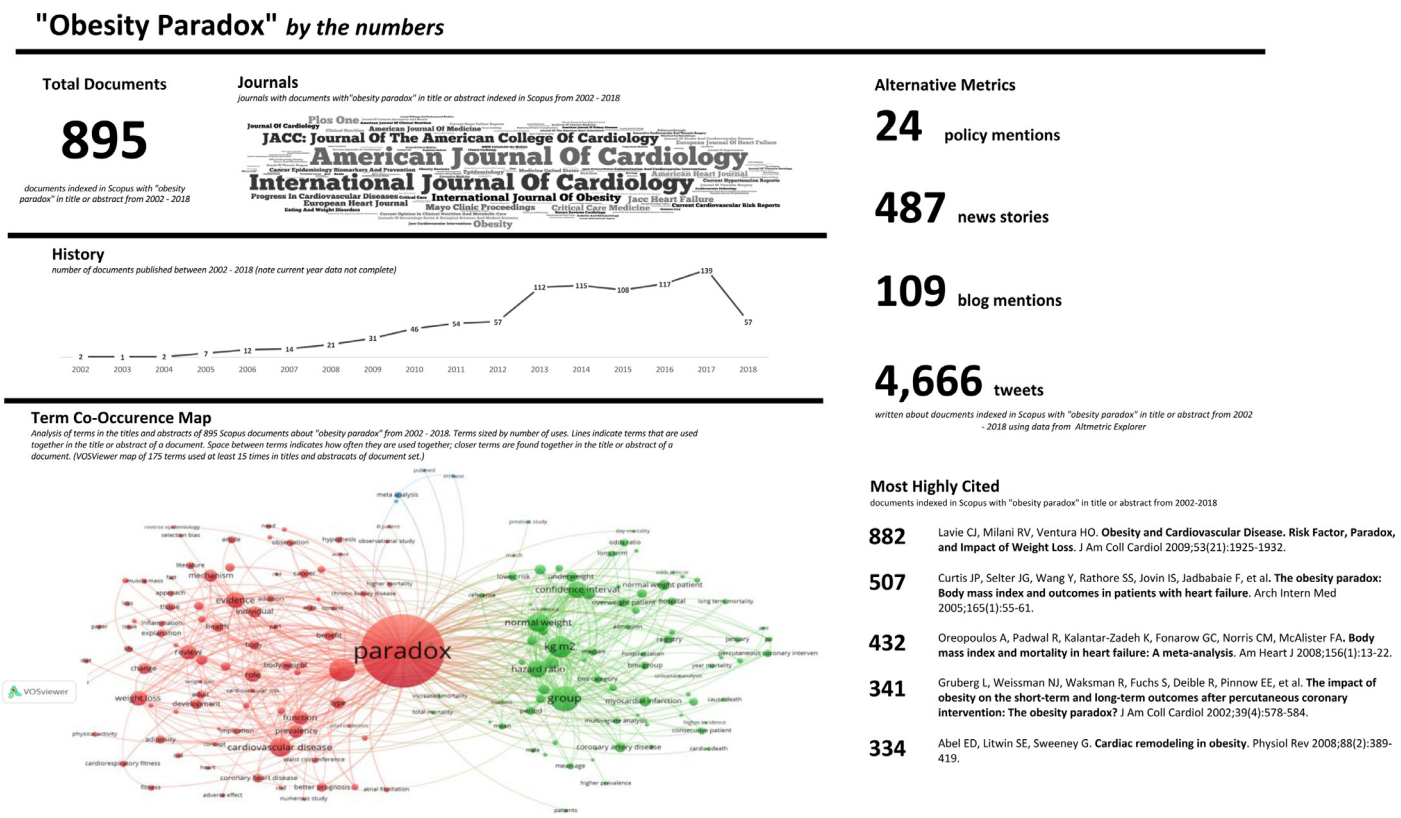

Fig. 1. Publication of research findings that include the terminology, obesity paradox, have risen rapidly over the past two decades with 895 documents indexed in Scopus with obesity paradox in title or abstract from 2000 to 2002. These manuscripts have attracted significant attention in the lay press with 487 news stories, 109 blog mentions, and 4666 tweets.

Similar results have been observed in patients with both HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) with lower or similar 30-day mortality in patients with higher BMI [24].

Non-Cardiovascular chronic disease states

Although the obesity paradox is well known in patients with CVD, the putative protective effects of overweight and obesity have also been observed in other chronic disease states. An early suggestion of an obesity paradox was rooted in a study performed in 1982 in a cohort of more than 1400 French patients demonstrating that overweight and obese patients with end-stage renal disease had lower overall and cardiovascular mortality, compared with normal weight patients [25]. In addition, this phenomenon has been observed in patients with chronic obstructive pulmonary disease (COPD), cirrhosis, diabetes, and cancer [26,27].

Explaining the obesity paradox in cardiovascular disease

Although an obesity paradox has been observed in patients with clinically manifest CVD and other chronic disease states, there are several factors that need to be considered when interpreting these findings and examining the adverse health effects of excess weight. These include the presence of comorbidities, confounders, selection bias, and use of BMI to classify excess weight, as discussed below.

Presence of comorbidities

Patients with prevalent CVD tend to be older and have a higher burden of comorbidities that may independently contribute to mortality [28]. In an analysis of 296,535 participants from the UK biobank, obesity was associated with increased risk of CVD and this association was further strengthened once participants with comorbidities were excluded suggesting that presence of comorbidities may also act as a confounder in the relationship between BMI and outcomes [29]. Lower BMI in patients with concomitant comorbidities, such as COPD, chronic kidney disease, liver disease, and malignancy, may reflect the severity of illness and frailty, and is associated with increased risk of cardiovascular disease. Rather than obesity conferring a protective advantage, weight loss due to illness resulting in a lower BMI prior to and after diagnosis of CVD may be a result of increased catabolic state or lack of metabolic reserve and associated with functional decline and poor quality of life. This reflects reverse causation whereby weight loss is a consequence rather than a cause of illness and is minimized when accounting for body weight throughout the life course. Men with constantly normal weight had the fewest comorbidities in late life and those with weight loss or constant overweight status had higher 12-year mortality rates compared with normal weight men in a longitudinal study investigating weight trajectories in 1114 men in the Helsinki Businessmen Study [30].

Confounding factors

Smoking status is an important source of two major biases in mortality analyses: reverse causation and confounding. As discussed above, reverse causation occurs because smoking is associated with greater risk of cardiovascular and non-cardiovascular comorbidities that predispose individuals to unintentional weight loss. Current smoking is also an important source of confounding as smoking is associated with lower BMI, but also with higher mortality rates due to cardiovascular and non-cardiovascular causes.

The impact of confounding with smoking has been demonstrated in several prior studies. In a study from NHANES III and 1999–2010 examining the association between weight status and mortality among individuals with CVD, mortality risks were significantly higher in the overweight and obese groups (HR 1.51; 95% CI 1.07, 2.15) in analyses confined to never-smokers [31]. Furthermore, in an analysis of more than 1.46 million individuals from the general population, restriction to never-smoking participants strengthened the mortality estimates in overweight (HR 1.13 [95% CI 1.09, 1.17]) and obese (HR ranging from 1.88 to 2.51 for BMI from 30.0 to 49.9 kg/m^2) groups using BMI 22.5–24.9 kg/m^2 as the reference category [32].

Cardiorespiratory fitness (CRF) and physical activity (PA) levels are strongly related to prognosis in patients with CVD and may attenuate the relationship between BMI and mortality [33]. There are numerous studies in primary prevention participants demonstrating the association of CRF and PA levels with all-cause mortality and cardiovascular morbidity, including incident CAD, HF, and atrial fibrillation [34]. However, data are limited among patients with prevalent CVD where CRF and PA may play a more prominent role. Among 855 patients referred for cardiac rehabilitation at the Mayo Clinic, individuals with who were overweight with low fitness had higher mortality than normal weight participants with high fitness [35]. Similarly, in 2066 patients with HFrEF, BMI was as significant predictor of survival in the low fitness group with worse outcomes in overweight ($\geq$25.0 kg/m^2) compared with normal BMI ($<$25.0 kg/m^2) [36]. In another analysis, when obese and lean patients with HFrEF were matched for peak VO_2, a measure of exercise tolerance, they had similar prognosis [37]. In a study of 6493 participants with coronary heart disease from the HUNT Study, BMI was not associated with survival among patients who were physically active [38]. In a follow-up analysis of 3307 participants from the same HUNT study, maintaining a high level of PA over 3 decades was associated with lower CVD mortality (HR 0.62; 95% CI: 0.43, 0.89) even after adjusting for changes in BMI [39]. These studies support the complex interplay between BMI, CRF, PA, and outcomes among patients with CVD.

Finally, residual confounding from unaccountable or unmeasurable variables may result in the demonstration of an inverse association between BMI and mortality in the setting of CVD, especially in retrospective studies and secondary data analyses.

Selection bias

One of the other potential explanations for the existence of the appearance of the obesity paradox is selection bias [40]. For example, selection or survival bias could occur if obese patients have earlier onset of disease and die at a younger age before they can be included in studies. The West of Scotland Coronary Prevention Study identified higher risk of fatal cardiovascular events in participants with BMI $\geq$ 30 kg/m^2 [41]. Given the increased risk of death from CV causes, obese participants are less likely to be enrolled in secondary prevention studies among CVD patients, resulting in the potential for survival and selection bias. Obese individuals are also more likely to be diagnosed with CVD at a younger age and spend more life years with CVD resulting in the appearance of an obesity paradox (Fig. 2). Recent data from the Cardiovascular Lifetime Risk Pooling Project demonstrated that overweight and obesity was associated with earlier onset of disease and increased burden of cardiovascular events even after adjusting for competing risk of non-cardiovascular events [4]. Following diagnosis of CVD, heavier individuals appeared to live longer on average compared to normal BMI individuals when BMI was measured at baseline prior to the onset of disease; but this occurred as a result of earlier onset of disease at a younger age and was a manifestation of lead-time bias, similar to the phenomenon observed in cancer screening diagnostics.

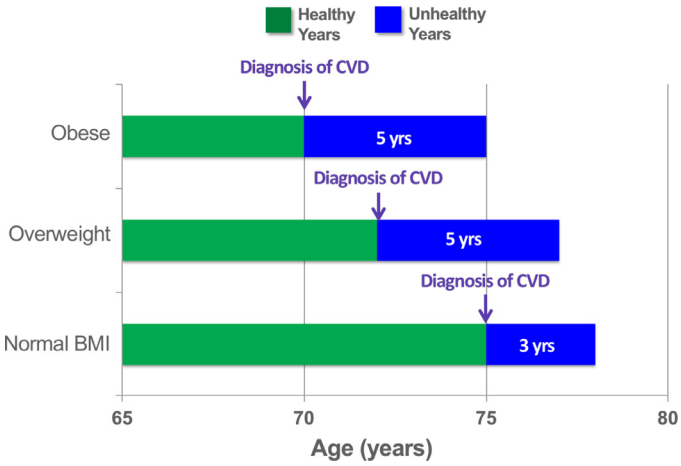

Fig. 2. A theoretical depiction utilizing a life course perspective of healthy and unhealthy years lived before and after diagnosis of CVD demonstrating an apparent obesity paradox due to an earlier onset of disease in individuals who are overweight or obese. This is similar to the concept of lead-time bias, which has been observed in cancer screening interventions, and highlights the importance of the life course perspective and incorporation of morbidity in understanding overall disease burden.

Additional anthropometric measures of excess weight

Although BMI is most commonly used to define obesity at the population level, prior studies have demonstrated the limitations of BMI as an incomplete measure of excess weight as it does not account for body composition or fat distribution. BMI is unable to distinguish between differences in muscle and fat mass or distribution of fat that may exacerbate or ameliorate CVD risk. When combined with BMI, measurement of WC may more accurately identify obese patients at risk for CVD. Current obesity guidelines define higher CV risk based on WC $\geq$ 40 inches in men and $\geq$35 inches in women respectively [8]. Specifically, higher waist circumference (WC) and body fat percentage have also been demonstrated to be associated with an greater risk of all-cause mortality and incident CVD [29,42]. In the Framingham study, greater visceral adiposity measured by computed tomography (CT) was associated with higher risk of incident CVD [43]. Recent data in patients with HFpEF demonstrated that all-cause mortality was significantly higher in patients with HFpEF and abdominal obesity compared with normal WC (HR 1.52 [95% CI: 1.16, 1.99]) [44].

Future directions

As obesity continues at epidemic levels at both the national and global level, understanding the role of obesity in the development and progression of CVD becomes increasingly important. While many studies have examined the relationship of BMI and mortality in patients with and without CVD, interventional studies assessing the cardiovascular benefits of intentional weight loss are urgently needed. This is especially important in patients with prevalent CVD where there appears to be equipoise. The Look AHEAD (Action for Health in Diabetes) trial demonstrated no difference in cardiovascular events in overweight or obese adults with type 2 diabetes at risk for CVD randomized to an intensive lifestyle intervention versus diabetes support and education control arm over a median follow-up of 9.6 years [45]. However large-scale studies in patients with prevalent CAD, HF, and other CV morbidities are lacking. In a prospective single center study, patients with CAD who experienced weight loss in a cardiac rehabilitation program had more

than 10% reduction in total mortality and acute CV events compared to the non-weight loss group [46]. A systematic review of therapeutic lifestyle changes in patients with CAD demonstrated lower risk of cardiovascular events in patients with intentional weight loss, but only 4 studies were included [47]. Prospective, randomized controlled trials with long-term follow up in large and diverse patient populations examining weight loss interventions are needed to help inform clinical practice guidelines in patients at risk for CVD and with prevalent CVD.

Conclusions

There is indisputable evidence demonstrating greater independent risk of incident CVD with obesity. However, the relationship between BMI and mortality in patients with prevalent CVD remains the subject of much debate. Many studies have observed lower mortality in obese patients with prevalent CVD (e.g. CAD, HF), which has resulted in unclear messaging about the true adverse health consequences of excess weight and confusion regarding clinical recommendations for weight loss. However, it is important to take into account the role of comorbidities, residual confounding, and selection bias that may limit the interpretation of these findings. Incorporation of additional anthropometric measures (e.g. WC, visceral fat on CT) may help to stratify risk in patients with obesity and CVD. Finally, there is a need for weight loss trials in patients with CVD to inform secondary prevention strategies in this group. Ultimately, efforts focused on primordial prevention (achieving and maintaining body weight prior to the development of CVD) are needed to promote healthier, longer lives free of CVD.

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