Turkish Journal of Thoracic and Cardiovascular Surgery 2024;32(1):1-8

ORIGINAL ARTICLE / ÖZGÜN MAKALE

Association of body mass index with clinical outcomes in patients with acute coronary syndrome: A systematic review and meta-analysis

Akut koroner sendromlu hastalarda vücut kütle indeksinin klinik sonuçlar ile ilişkisi: Sistematik derleme ve meta-analiz

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ABSTRACT

Background: In this meta-analysis, we aimed to systematically examine the relationship between body mass index and major adverse cardiovascular events in acute coronary syndrome patients and to provide theoretical guidance for body weight management in these patients.

Methods: A comprehensive analysis of applicable research published between 2008 and 2021 was conducted using the PubMed, Cochrane, Web of Science, Wanfang, and CNKI databases. Extracted odds ratios from the randomized-controlled studies were pooled using fixed-effects meta-analysis. Publication bias was addressed through evaluation methods such as funnel plot or sensitivity analysis.

Results: Ten studies with a total of 58,992 individuals were included. The consequences of this meta-analysis confirmed that, compared to normal body mass index, patients with acute coronary syndrome significantly increased the risk of major adverse cardiovascular events (odds ratio= 1.20; 95% confidence interval: 1.12-1.29, p<0.001).

Conclusion: Patients with acute coronary syndrome being overweight or obese significantly increased the risk of major adverse cardiovascular events compared to those with normal body mass index. The results suggest that patients may focus on weight management to reduce the risk of major adverse cardiovascular events in acute coronary syndrome.

Keywords: Acute coronary syndrome, body mass index, major adverse cardiovascular event, meta-analysis.

ÖZ

Amaç: Bu meta-analizde, akut koroner sendrom hastalarında vücut kütle indeksi ve majör advers kardiyovasküler olaylar arasındaki ilişki sistematik olarak incelendi ve bu hastalarda vücut ağırlığı yönetimine yönelik teorik rehber oluşturuldu.

Çalışma planı: 2008-2021 yılları arasında yayımlanan uygulanabilir çalışmaları kapsamlı bir şekilde analiz etmek için PubMed, Cochrane, Web of Science, Wanfang ve CNKI veri tabanları kullanıldı. Randomize kontrollü çalışmalardan elde edilen olasılık oranları, sabit etkili meta-analizler kullanılarak bir araya getirildi. Yayın yanlılığı, huni grafikleri veya duyarlılık analizleri gibi değerlendirme yöntemleri ile ele alındı.

Bulgular: Toplam 58.992 kişiden oluşan 10 çalışma dahil edildi. Bu meta-analizin sonuçları, akut koroner sendromlu hastalarda majör advers kardiyovasküler olay riskinin normal vücut kütle indeksi ile karşılaştırıldığında anlamlı derecede arttığını doğruladı (olasılık oranı= 1.20; 95% güven aralığı: 1.12-1.29, p<0.001).

Sonuç: Vücut kütle indeksi normal olanlara kıyasla, fazla kilolu veya obez olan akut koroner sendromlu hastalarda majör advers kardiyovasküler olay gelişme riski anlamlı olarak artmıştır. Sonuçlar, hastaların akut koroner sendromlu hastaların majör advers kardiyovasküler olay riskini azaltmak için kilo yönetimine dikkat etmeleri gerektiğini göstermektedir.

Anahtar sözcükler: Akut koroner sendrom, vücut kütle indeksi, majör advers kardiyovasküler olay, meta-analiz.

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Doi: 10.5606/tgkdc.dergisi.2024.24405

Received: November 10, 2022
Accepted: September 21, 2023
Published online: January 10, 2024

Cite this article as: Wang M, Wei X, Zhao M. Association of body mass index with clinical outcomes in patients with acute coronary syndrome: A systematic review and meta-analysis. Turk Gogus Kalp Dama 2024;32(1):1-8. doi: 10.5606/tgkdc.dergisi.2024.24405.

Acute coronary syndrome (ACS) comprises unstable angina, non-ST elevated myocardial infarction (MI), or ST-elevated MI[1] and it causes a significant morbidity and mortality and economic burden.[2] Rapid reperfusion with essential percutaneous coronary intervention (PCI) within 120 min, when ST-segment elevation MI (STEMI) is diagnosed via electrocardiography can decrease mortality from 9 to 7%. If PCI is not available within 120 min, thrombolytic therapy with a full dose of alteplase, reteplase, or tenecteplase should be administered to patients under 75 years of age without contraindications. For patients aged 75 years or older, a half dose should be given followed by transfer to a PCI-targeted facility within the next 24 h.[3]

As recommended by the World Health Organization (WHO), body mass index (BMI) is categorized as underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obesity (>30 kg/m^2).[4] Some studies have shown a lower mortality in individuals with obesity with cardiovascular disease (CVD), and moderate and severe obesity are associated with poorer survival in patients with ACS.[5] Obesity has been identified as an independent risk factor for coronary artery disease (CAD).[6] However, it is unclear whether the occurrence of major adverse cardiovascular events (MACEs) is associated with increasing weight compared to the BMI=18.5 to 24.9 kg/m^2 (considered as normal weight) in ACS.

In this meta-analysis, we aimed to systematically examine the relationship between BMI and MACE in ACS patients, to provide theoretical guidance for clinical weight management in ACS patients and help to avoid the occurrence of MACEs.

MATERIALS AND METHODS

The findings were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[7] Publication bias was addressed through the evaluation methods such as funnel plot and Egger's regression asymmetry. We conducted a comprehensive search of PubMed, Cochrane, Web of Science, Wanfang Data, and CNKI databases from 2008 to 2021 using a combination of terms related to BMI, obesity, body weight, MI, ACS, death, mortality and CAD. Two reviewers independently recognized articles and sequentially screened them for inclusion, starting with titles and abstracts and, then, full-text review. In addition, references to retrieved publications were carefully reviewed to identify any studies that might have been missed. Any disagreements in the data extraction process are arbitrated by the third investigator.

Inclusion criteria

Inclusion criteria were as follows: *(i)* randomized-controlled trials; *(ii)* an objective to examine an effect on BMI on early or long-term outcomes in patients with ACS; and *(iii)* data of MACEs in different BMI groups. Exclusion criteria were as follows: *(i)* the sample size was less than 100; *(ii)* studies not conducted on BMI subgroups; *(iii)* MACEs not included in the outcome metrics; *(iv)* reviews or meeting abstract.

Data extraction and quality assessment

Three authors independently extracted the records by using the aforementioned criteria. The following objects were abstracted from the included studies: first author's surname, publication year, the number of patients, mean age of patients, study period, the objective of studies, BMI categories, study design, follow-up period, and clinical outcomes. There was no significant difference in data extraction among the three authors.

Statistical analysis

Statistical analysis was performed using the Stata 14.0 software (StataCorp LLC, College Station, TX, USA). The combined odds ratio (OR) and 95% confidence interval (CI) were calculated using variance inverse weighted random effects model. The normal BMI group was selected as the reference group. Heterogeneity between studies was assessed using the Cochran Q test and the I^2 statistic, which indicates that the percentage of total variation between the studies was the result of heterogeneity rather than chance. The I^2 values representing moderate (30 to 60%), substantial (50 to 90%), and considerable (75 to 100%) heterogeneity were based totally on the Cochrane Collaboration recommendations.[8] A p value of <0.05 was considered statistically significant. The Begg and Mazumdar rank correlation tests and Egger's regression intercept tests were used for publication bias tests. In case of significant deviations, the pruning and filling methods of Duval and Tweedie were used to correct the asymmetry of the funnel plot. The effect of individual studies was examined by exclusion sensitivity analysis. Each study was removed at a time to assess the extent to which meta-analysis estimates relied on that particular study. Forest maps were used to express the results of the meta-analysis.

Table 1. The characteristics of the 10 studies

Author (year)	Total (n)	Mean age (year)	Study period	BMI categories	Study design	Objective	Follow-up period	Outcomes
De Luca et al.[11] 2020	1,408	79.5	NA	BMI <25.7, BMI ≥25.7	A randomized, open-label, blinded endpoint study	To compare low-dose (5 mg) prasugrel vs clopidogrel among elderly patients with ACS	12-month	Cardiovascular mortality
Kadakia et al.[17] 2011	6,560	64.3	NA	three BMI groups (<25, 25-30, ≥30)	A randomized trial	To determine whether this 'obesity paradox' persists in the long term and to examine the specific relationship of central obesity with outcomes after ACS.	30 days	Cardiovascular death, MI or recurrent ischaemia
Lin et al.[18] 2013	1,347	65.6	1997-2003	BMI ≥25 (overweight/ obese) or BMI <25 (normal/underweight)	NA	To evaluate the impact of HDL-C and BMI on mortality among CAD patients	5.3 years	Cardiac and all-cause death
Lopez-Jimenez et al.[13] 2008	2,481	61.3	NA	Underweight (BMI <20), normal weight (BMI ≥20 but <25, overweight (BMI ≥25 but <30), obese (BMI ≥30 but <40), and morbidly obese (BMI ≥40).	Randomized clinical trial	To assess weight change, and the associations of baseline weight and change at follow-up outcomes and interactions between psychosocial factors.	29 months	All-cause mortality, recurrent MI, coronary revascularization and cardiac hospitalizations.
Mak et al.[16] 2009	15,532	64.3	NA	Quartile 1 (12.96-25.08), Quartile 2 (25.09-27.86), Quartile 3 (27.87-31.27), Quartile 4 (31.28-67.77)	A prospective observational study	To determine the relationship between BMI and cardiovascular events among individuals	28 months	Cardiovascular death, MI, or stroke, all-cause mortality, and bleeding complications.
Samanta et al.[9] 2020	2,913	59.14	2004-2014	Normal (18.5-24.9), overweight (25-29.99) and obese (≥30)	NA	To assess the influence of BMI on early and long-term outcomes in patients with MI and left ventricular dysfunction	At 1, 6, and 12 months	Death and recurrent acute myocardial infarction were the major endpoints in the analysis
Sarno et al.[10] 2010	1,707	NA	November 27, 2006, to May 18, 2007	Normal (<25), overweight (25 to 30), or obese (>30)	A randomized trial	To assess the effect of BMI on 1-year outcomes in patients enrolled in a contemporary percutaneous coronary intervention trial comparing a sirolimus-eluting stent with a durable polymer to a biolimus-eluting stent with a biodegradable polymer.	1 year	Cardiac death, MI, and clinically justified target vessel revascularization

Table 1. Continued

Author (year)	Total (n)	Mean age (year)	Study period	BMI categories	Study design	Objective	Follow-up period	Outcomes
Volkers et al.[12] 2017	1,969	68.9	NA	four BMI groups <20, 20-25, 25-30, and ≥30	Randomized trial	To determine whether the obesity paradox exists in patients who undergo carotid artery stenting or carotid endarterectomy for symptomatic carotid artery stenosis	2 years	Stroke or death
Wolny et al.[14] 2020	22,922	62.8	1999-2016	Underweight (BMI <18.5), normal weight (18.5 ≤BMI <25), overweight (25 ≤BMI <30), and obese (Class I [30 ≤BMI <35], Class II [35 ≤BMI <40], or Class III [BMI ≥40])	Randomized controlled trial	To evaluate the relationship between BMI and outcomes in patients with coronary artery disease undergoing percutaneous revascularization	5 years	All cause death at five years. Cardiac and non-cardiac death, target (TLR) and nontarget lesion revascularization (NTLR), MI, and definite/probable stent thrombosis.
Xing et al.[15] 2019	2,153	58.6	NA	Normal, 18.5 ≤BMI <25; overweight, BMI: 25-29.99; obese, BMI ≥30	A randomized trial	To investigate the effects of BMI on the primary endpoint and the secondary endpoint in the population	2.9 years	All-cause mortality, cardiac death, non-cardiac death, or New York Heart Association class IV heart failure

BMI: Body mass index; MI: Myocardial infarction; ACS: Acute coronary syndrome; CAD: Coronary artery disease; NA: Not applicable.

RESULTS

Literature retrieval and research traits

A total of 4,220 records were identified by searching the electronic databases, with 1,239 records remained after excluding the duplicates. Twenty-eight articles were eligible for further full-text evaluation after scanning the titles and abstracts. Seventeen articles were further removed due to ineligibility, lack of data, partial publication or lack of full access. As shown in Table 1, finally 10 studies[9-18] were included in this meta-analysis (Figure 1). The specific quality evaluation table of the included literature is shown in Figure 2.

BMI and the occurrence of MACEs

As shown in Figure 3, 10 researches recruiting 58,992 participants reported the association between altered BMI and the risk of MACEs in patients with ACS. Due to the low overall heterogeneity (χ^2=13.04; df=9; I^2=31%), fixed-effect model was used to evaluate this study. Compared to normal BMI, overweight or obesity in patients with ACS were significantly increased the risks of the occurrence of MACEs (OR= 1.20; 95% CI: 1.12-1.29, p<0.001).

Sensitivity analysis

The sensitivity analysis showed that when each study was individually removed from the analysis, no evidence

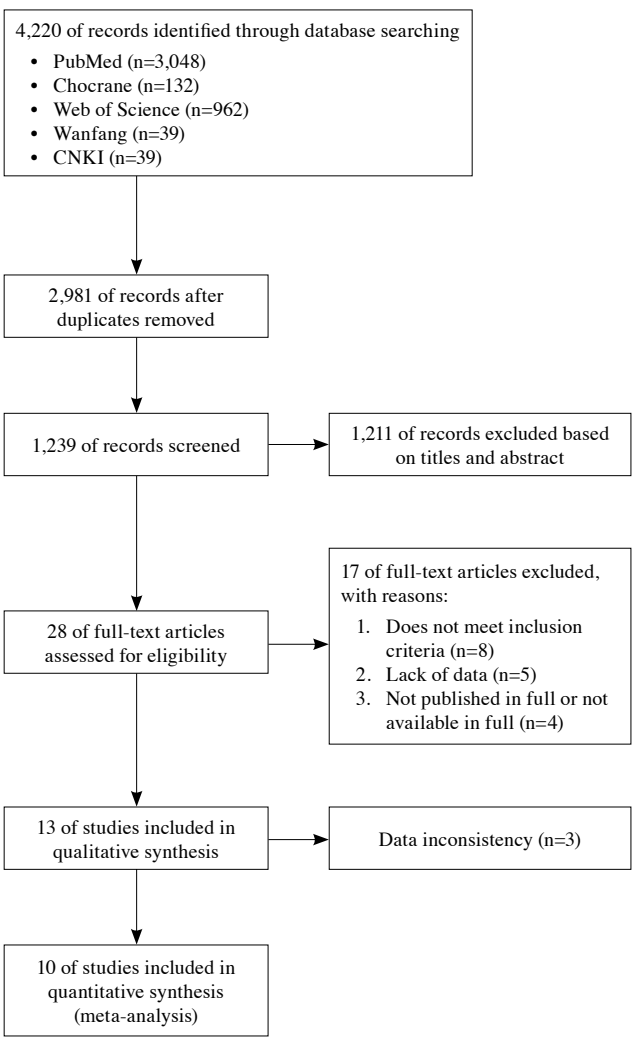

Figure 1. Flow chart of studies selection process.
CNKI: China Knowledge Resource Integrated.

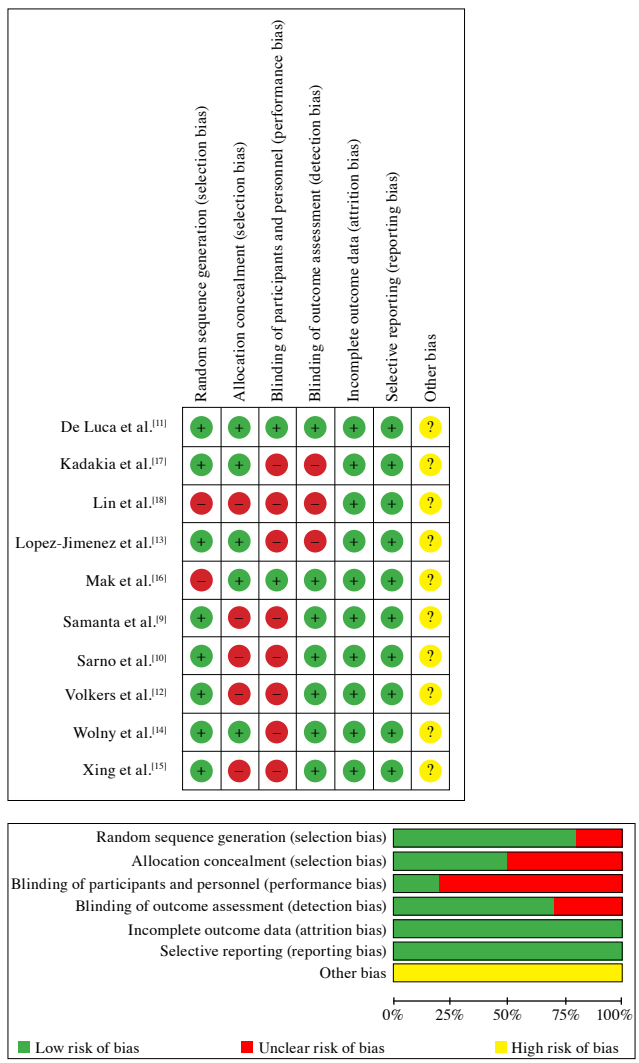

Figure 2. The risk of bias summary of review authors judgments.

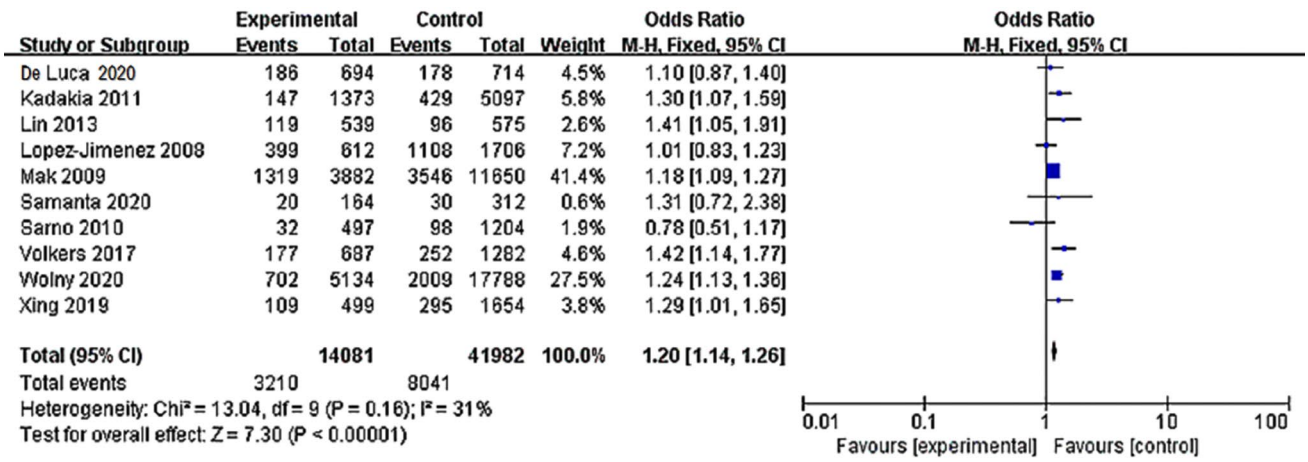

Figure 3. The forest plot of BMI and the risk of MACE in patients with ACS.

CI: Confidence interval; BMI: Body mass index; MACE: Major adverse cardiovascular events; ACS: Acute coronary syndrome.

of changes in the overall outcome was observed, as shown in the funnel plot of publication bias in Figure 4.

DISCUSSION

Obesity, described as a higher BMI, is considered a risk factor for mortality in the general population. In this meta-analysis, patients with ACS who were overweight or obese showed a significantly higher risk of MACEs than those with normal BMI ($p<0.001$). The relationship between overweight or obesity and the occurrence of MACEs is consistent with a previous study,[19] which revealed that increased BMI after ACS was associated with the increased adjusted survival compared to normal BMI. It is necessary to note that patients with obesity are more likely to have diabetes and/or hypertension, but they are younger and have fewer bleeding complications, which may affect their survival.[20] Compared to patients with normal weight, patients with low BMI have the highest risk of death, and those with overweight, obesity and severe obesity have lower mortality.[20] However, patients with diabetes, hypertension or hyperlipidemia with BMI ≥25 kg/m^2 have a higher cardiovascular risk than those with normal BMI,[20] which is consistent with our findings.

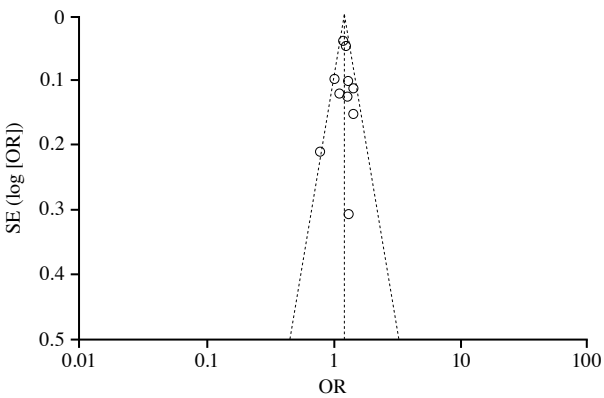

Figure 4. Funnel plot for publication bias. OR represents odds ratio.

SE: Standard error; OR: Odds ratio.

According to the "obesity paradox", adults with obesity have a survival advantage after ACS compared to those without. A prospective study showed that the higher survival of overweight or obese patients may be due to the relatively short follow-up period in the study, with a little chance of diabetes or hypertension causing complications and affecting mortality during hospitalization or even up to five years after MI.[21] Obesity may have decreased in-hospital mortality, while intense weight problems were related to the increased in-hospital mortality rates.[22] Of note, these studies have cautioned that weight problems and intense weight problems are associated with an increased complication burden of ACS.[21,22] Similarly, Alfadhel et al.[23] revealed an increased risk of all-cause mortality in patients who presented with ACS and underwent coronary angiography in patients with a very low or very high BMI, and there was no decrease in the mortality rates among the mildly obese individuals. Furthermore, there are studies showing that BMI is no longer related to a greater 30-day risk of cardiovascular outcomes in patients admitted to the emergency room with potential ACS.[24] Other studies analyzing risk factors for ACS in patients under 40 years of age have demonstrated

obesity as the most common risk factor among young individuals with ACS,[25] consistent with our study results showing a positive association between BMI and MACE occurrence. In addition, individuals with a higher BMI are at a greater risk of developing CVD, including MACEs, than those with a lower BMI. This relationship between BMI and MACEs appears to be non-linear, with the risk increasing more steeply in the obese range of BMI (≥30 kg/m^2). However, it is important to note that BMI is not a perfect predictor of MACE, and other factors, such as genetics, lifestyle choices, and preexisting medical conditions, may also play a role in an individual's risk for CVD. To date, the role of obesity on cardiovascular outcome in hospitalized individuals with ACS has been controversial, depending on the extent of obesity and duration of follow-up, as well as the effect of different degrees of obesity. Additionally, other measures of body composition, such as waist circumference or body fat percentage, may be better predictors of cardiovascular risk than BMI alone.

The main limitation to this study susceptible to many sources of bias. First, the sample sizes included in the studies were inconsistent, with some being too large. Second, there is no recent literature related to this study. Third, our study was unable to explain the relationship between BMI and the occurrence of MACE, when BMI was less than 25. Although this limitation may affect causal inference, our results are still informative.

In conclusion, our data show that body mass index has a significant impact on the occurrence of major adverse cardiovascular events in patients with acute coronary syndrome. Overweight and obesity significantly increase the risk of major adverse cardiovascular events in these patients. Based on our meta-analysis results, we suggest that weight management may be necessary to reduce the risk of major adverse cardiovascular events in patients with acute coronary syndrome.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Collaborated on the design: M.W., X.W.; Leading data collection: M.W.; Participated in data analysis and interpretation: X.W.; Took the lead in writing the article: M.W.; Conducted the critical review: X.W., M.Z.; Managed references, fundings, materials, and provided supervision: M.Z.; All authors contributed to the study idea and concept. All authors read and approved the final manuscript.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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