What are the real associations of homeostasis model assessment (HOMA) with body mass index and age?

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Abstract

Introduction: Insulin resistance (IR), a key pathogenesis mechanism of metabolic disorders, can be tested using homeostatic model assessment (HOMA). HOMA-IR quantifies peripheral tissue IR, whereas HOMA-β determines insulin secretion. The cross-sectional study aimed to examine non-linear associations of HOMA indices with age when adjusting for body mass index (BMI), and thus to investigate the indices' ability to reflect the real development of glucose metabolism disorders over time.

Material and methods: The sample comprised 3406 individuals without diabetes mellitus (DM) divided into those with normal glucose metabolism (NGT, n = 1947) and prediabetes (n = 1459) after undergoing biochemical analyses. Polynomial multiple multivariate regression was applied to objectify associations of HOMA with both age and BMI.

Results: Mean values of HOMA-IR and HOMA-β in individuals with NGT were 1.5 and 82.8, respectively, while in prediabetics they were 2.2 and 74.3, respectively. The regression proved an inverse non-linear dependence of pancreatic β dysfunction, expressed by HOMA-β, on age, but did not prove a dependence on age for HOMA-IR. Both indices were positively, statistically significantly related to BMI, with a unit increase in BMI representing an increase in HOMA-IR by 0.1 and in HOMA-β by 3.2.

Conclusions: The mean values of HOMA indices showed that, compared with NGT, prediabetes is associated with more developed IR but lower insulin secretion. Both HOMA-IR and HOMA-β are predicted by BMI, but only HOMA-β is predicted by age. HOMA indices can reflect non-linear, closer-to-reality dependencies on age, which in many epidemiological studies are simplified to linear ones. The assessment of glucose metabolism using HOMA indices is beneficial for the primary prevention of IR and thus DM. **(Endokrynol Pol 2022; 73 (4): 736–742)**

Key words: insulin resistance; prediabetes; diabetes mellitus; homeostasis model assessment

Introduction

The increasing prevalence of diabetes mellitus (DM) and its pre-stage prediabetes is a major global health problem. The early detection and treatment of prediabetes can delay the onset of DM and thus present an important DM prevention strategy. High incidence of DM shows that there are missed opportunities for prediabetes management in primary care. Healthcare providers need to change their approach to prediabetes and play a more effective role in preventing DM [1–3].

The essence of the prevention is the early detection and quantification of insulin sensitivity or insulin resistance (IR), inversely, which is a key pathogenesis mechanism of both prediabetes and DM [3]. Several techniques are available for making measurements of IR, including precise clamp techniques. These techniques, however, are complicated, cumbersome, and, in general, not suitable for routine clinical work or large-scale population studies. For these reasons, a wide variety of indices based on simpler clinical measurements have been proposed for assessing IR. Homeostatic model assessment (HOMA) is a method used to quantify IR (HOMA-IR) and beta-cell function (HOMA-β) [4]. Its satisfactory correlation with the accurate glucose clamp techniques has been confirmed by numerous studies [5].

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In their previous work, the authors dealt with the relationship between HOMA and other parameters, usually determined in clinical practice. Thus, statistically significant linear associations of HOMA with some parameters were demonstrated, including the inverse linear association of HOMA-β with age. Such an association with age was not proven for HOMA-IR [6, 7]. However, it is assumed that the dependence of the development of glucose metabolism disorders, including IR and β-cell dysfunction, on time (expressed by the increasing age), is not a linear function. This is a non-linear relationship with the achievement of a certain peak followed by a decrease, and often presumed linearity is a limitation of many epidemiological studies [8]. It remains debatable whether HOMA indices can accurately reflect this real non-linear dependence, which is the focus of the present work.

This cross-sectional study aimed to examine the non-linear associations of HOMA indices with age when adjusting for body mass index (BMI), and thus to investigate the indices' ability to reflect the real development of glucose metabolism disorders over time in a robust sample of obese individuals without DM. The aim was also to point out the possibility of using HOMA to identify individuals at risk for developing impaired insulin sensitivity.

Material and methods

Study population

The sample comprised all individuals registered in an outpatient internal medicine centre in *Outpatient Medicine Center in Hradec Kralove*, Czech Republic. After undergoing anthropometric and laboratory analyses and with respect to patients' history, all individuals without DM (n = 3406) were enrolled between 2009 and 2015. The sample was divided into 2 subgroups: subjects with normal glucose tolerance (NGT, n = 1947) and prediabetics (n = 1459). The prediabetics were individuals with at least one of the following conditions: (1) fasting plasma glucose 5.6–6.9 mmol/L; (2) 120-minute plasma glucose 7.8–11.0 mmol/L after a 75 g oral glucose tolerance test (OGTT). Individuals in the NGT subgroup included the other patients attending the centre with normal glucose metabolism. None of the participants received long-term therapy with oral antidiabetic drugs. Individuals with at least one missing value of interest were excluded; thus, only complete observations were included.
The study was conducted according to the principles stated in the Declaration of Helsinki. The study was approved by the Ethics Committee of -ANONYMYZED- (Approval No. 20/11). To be included in the study, all subjects signed informed consent forms

Laboratory analysis

Venous blood samples were drawn in the morning after a 12-hour fast. After centrifugation, the serum was used for analyses on the day of blood collection. Routine serum biochemical parameters were analysed on a COBAS 8000 (Roche Diagnostics GmbH, Manheim, Germany). Insulin was determined by the Chemiluminescent Microparticle Immunoassay method on an Architect i1000SR (Abbott Laboratories, Chicago, IL, USA). All analyses were performed according to the manufacturer's instructions and after verification of methods.

Statistical analysis

Statistical analysis was performed using the computing environment R (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). HOMA-IR indices were calculated with the following formulas (glucose levels in mmol/L, insulin levels in mIU/L) [5]:
Extreme values of glucose and insulin, limiting the use of HOMA, were found and excluded using the inner and outer fences method. The Wilcoxon signed-rank test was used to compare numerical characteristics between the given subgroups to obtain the statistical significance of differences (p-value). Polynomial multiple multivariate regression was applied to objectify associations of response variables, HOMA indices, and explanatory variables, age, and BMI. To explore tendencies of HOMA indices, both increasing and decreasing, with age, we used squared polynomial relation. BMI, the other explanatory variable, was involved to adjust the indices' dependence on anthropometric variables. The level of statistical significance was set at $p < 0.05$.

Results

Characteristics of the study population

Table 1 presents the basic characteristics of study subjects. All examined variables differed statistically significantly between the NGT and prediabetic subgroups. The study population consisted of middle-aged people with obesity, which was significantly more pronounced in the case of prediabetics. Blood serum glucose values, both fasting and at 60 and 120 minutes of OGTT, were higher, above the upper reference limit, in prediabetics compared to subjects with NGT. Insulinaemia, C-peptide, and HOMA-IR were also higher in prediabetics, while HOMA-β was higher in individuals with NGT. Thus, the mean values of the HOMA indices showed that, compared with NGT, prediabetes was associated with more developed IR but lower insulin secretion. For all observed characteristics, more abnormal values were recorded in males than in females. Both HOMA indices showed higher values in men.

Regression analysis

Polynomial multiple regression showed a statistically significant linear dependence of both HOMA indices on BMI and a quadratic dependence of HOMA-β on age (Tab. 2). A unit increase in BMI constitutes an increase in HOMA-IR by 0.1 and in HOMA-β by 3.2 (Fig. 1, 2). Graphic representation of the quadratic dependence of HOMA-β on age creates a parabola, showing the increase and decrease of the index values around a time peak (Fig. 3).

Discussion

The obtained results demonstrate a dependence of both HOMA indices on BMI and an inverse dependence of HOMA-β on age. There is a clear association between BMI and HOMA, which, regardless of age, is manifested by an adverse increase in IR with growing

Table 1. *Basic characteristics of the study population (mean value, 95% confidence interval of the mean)*

Characteristics	Normal glucose tolerance			Prediabetics		
	All	**Females**	**Males**	**All**	**Females**	**Males**
N [females, males]	1947	1590	357	1459	1047	412
Age [years]	38.5 (38.0–39.1)	38.1 (37.5–38.6)	40.6 (39.2–42.0)	44.0 (43.4–44.6)	44.1 (43.3–44.8)	43.9 (42.8–45.0)
Glucose [mmol/L]	5.15 (5.11–5.18)	5.10 (5.07–5.13)	5.37 (5.24–5.50)	5.82 (5.79–5.84)	5.77 (5.74–5.80)	5.93 (5.89–5.97)
Glucose 60-minute OGTT [mmol/L]	7.30 (7.16–7.44)	7.17 (7.02–7.32)	7.71 (7.41–8.01)	9.36 (9.14–9.57)	9.23 (8.98–9.48)	9.62 (9.22–10.01)
Glucose 120-minute OGTT [mmol/L]	6.71 (6.55–6.86)	6.60 (6.46–6.74)	6.99 (6.80–7.18)	8.90 (8.73–9.07)	8.75 (8.66–8.94)	9.23 (8.61–9.85)
Insulin [mIU/L]	7.93 (7.67–8.19)	7.51 (7.26–7.76)	9.80 (8.96–10.65)	10.73 (10.12–11.34)	10.35 (9.57–11.12)	11.74 (10.87–12.61)
C-peptide [ng/mL]	702.53 (686.81–718.25)	670.22 (654.48–685.95)	846.67 (800.02–893.31)	907.59 (883.46–931.72)	868.34 (840.59–896.08)	1007.13 (960.19–1054.07)
HOMA-IR	1.47 (1.43–1.51)	1.41 (1.36–1.45)	1.78 (1.64–1.93)	2.17 (2.10–2.25)	2.09 (2.01–2.18)	2.40 (2.23–2.59)
HOMA-β	82.77 (80.25–85.37)	81.55 (78.88–84.32)	88.51 (81.68–95.92)	74.25 (71.64–76.95)	73.55 (70.57–76.66)	76.10 (70.91–81.66)
BMI [kg/m²]	31.60 (31.26–31.94)	31.31 (30.93–31.70)	32.87 (32.14–33.61)	35.04 (34.65–35.42)	34.68 (34.24–35.12)	35.95 (35.17–36.72)

N — number; OGTT — oral glucose tolerance test; HOMA — homeostatic model assessment; IR — insulin resistance; BMI — body mass index; HOMA-β — HOMA of beta cell function

Table 2. *Regression analysis of the dependence between homeostatic model assessment (HOMA) and explanatory variables — age, body mass index (BMI)*

Explanatory variables	Estimate	Std. Error	t-value	p-value
Response variable HOMA-IR				
Intercept	−1.418	0.174	−8.144	< 0.0001
Age (squared)	−0.001	0.373	−0.532	0.595
BMI	0.112	0.505	22.237	< 0.0001
Response variable HOMA-β				
Intercept	21.522	8.599	2.503	0.012
Age (squared)	−0.01433	0.002	−7.789	< 0.0001
BMI	3.231	0.249	12.962	< 0.0001

IR — insulin resistance; HOMA-β — HOMA of beta cell function

BMI. Conversely, increased age itself does not mean an increase in IR but manifests itself in a decrease in insulin secretion by β cells, which corresponds to the assumption of endocrine function reduction of the pancreas in the elderly [9]. Demonstration of these, to some extent, expected conclusions using HOMA indices confirms their high diagnostic accuracy and their ability to serve as an effective, clinically available tool for objectifying IR. The greatest importance of the early diagnosis of impaired insulin sensitivity and IR in clinical practice lies especially in the primary prevention of DM. In addition to basic risk factors such as age, family history, elevated triglycerides, elevated

systolic blood pressure, and obesity, it is useful to specifically target people with incipient defects in insulin secretion or sensitivity.

Our study group consisted of people who, in terms of prediction, represented individuals at potential cardiometabolic risk, even though they did not have overt DM at the time of data collection. All individuals were obese, with OGTT in the prediabetic group indicating an incipient impaired glucose tolerance. HOMA-β was significantly lower in prediabetics than in those with NGT. Many studies point out that the time trajectory of plasma glucose levels, insulin secretion and IR run unevenly fast before the diagnosis of DM. About 7
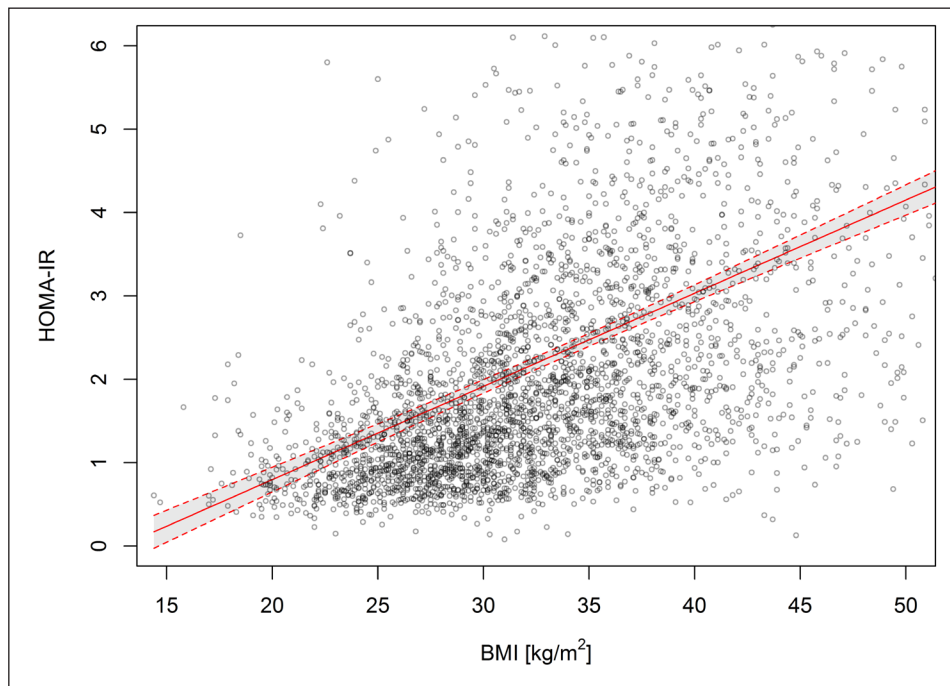
Figure 1. *Scatter diagram showing a linear association of body mass index (BMI) and homeostasis model assessment for insulin resistance (HOMA-IR) (with 95% confidence bands for the medians of variables on the y-axis for a given variable on the x-axis)*
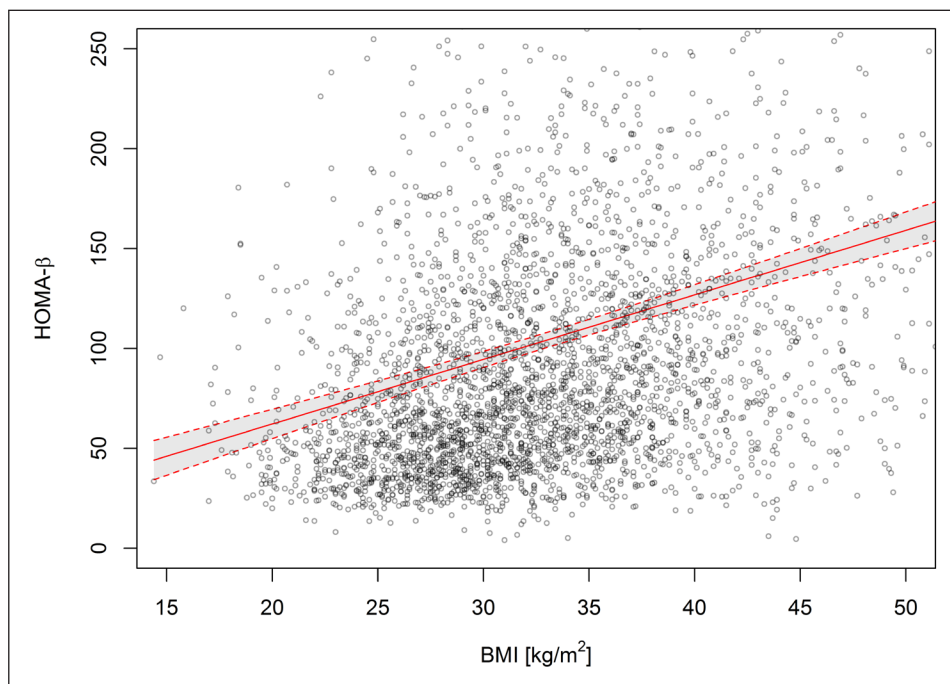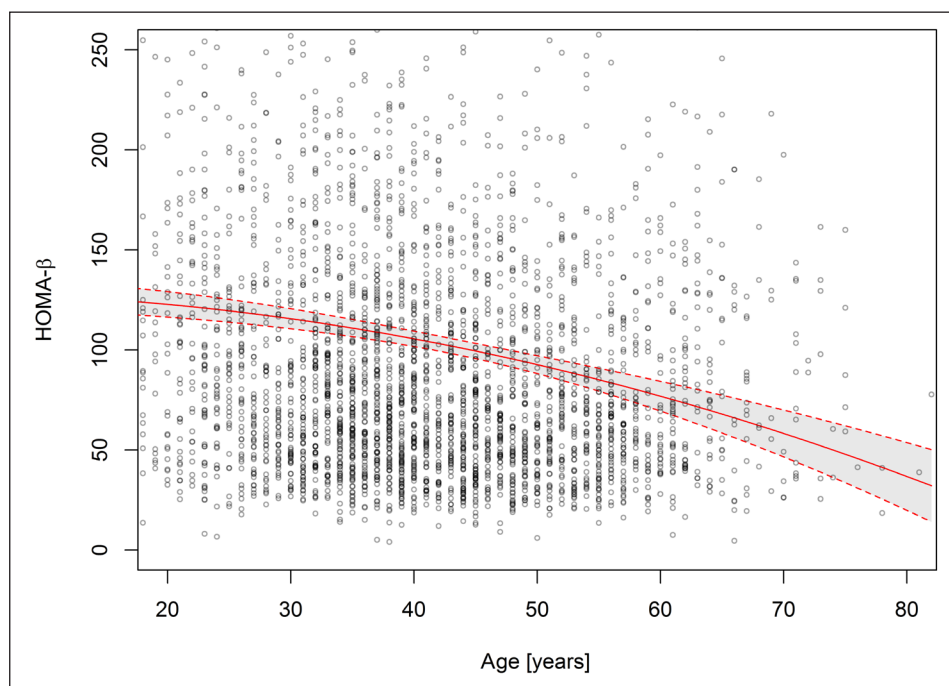

Figure 2. *Scatter diagram showing a linear association of body mass index (BMI) and homeostasis model assessment for β-cell function (HOMA-β) (with 95% confidence bands for the medians of variables on the y-axis for a given variable on the x-axis)*

years before the diagnosis of DM, HOMA-β increases until the diagnosis itself and then decreases. This "compensatory" period with increased insulin secretion, which is characterized by the various trajectories of insulin sensitivity and its secretion, is crucial

for the optimal timing of screening and preventive measures [10]. Epidemiological studies of high-risk individuals with varying degrees of impaired glucose metabolism demonstrate potential uses (in addition to plasma glucose values) of C-peptide levels and HOMA

Figure 3. *Scatter diagram showing a non-linear (parabolic) association of age and homeostasis model assessment for β-cell function (HOMA-β) (with 95% confidence bands for the medians of variables on the y-axis for a given variable on the x-axis)*

indices for controlling IR development. Subjects with HOMA-β lower than 73.0 are considered defective in insulin secretion [11]. In the present study, the group of prediabetics approached this value. In individuals with a relatively mild defect in insulin secretion, fasting levels of C peptide are increased, which was also shown in our group, in which the levels of C peptide in both women and men were higher than 600 ng/mL. Many studies have examined the role of pancreatic β cell and IR dysfunction in the pathophysiology of newly diagnosed DM. During the progression from NGT to DM, HOMA-IR increases, while HOMA-β decreases significantly [10]. Both indices can therefore be used for the early detection of glucose metabolism disorders.

IR is primarily manifested by fasting hyperglycaemia, while β-cell dysfunction, the predominant impairment of insulin secretion, is manifested by marked hyperglycaemia after glucose exposure [12]. In prediabetics of our study, the glycaemia at 120 minutes of OGTT was higher than 7.8 mmol/L, which corresponds to the state of developed IR, as demonstrated by a higher mean HOMA-IR value compared to individuals with NGT. At the same time, the prediabetics already had altered β cells, as shown by their lower mean HOMA-β value compared to NGT individuals. Moreover, all the study subjects were obese. Obesity with excessive accumulation of lipids in adipocytes and its infiltration by immune cells as a consequence of hypoxia significantly contributes to the development

of IR. Reducing adipose tissue expansion is one of the main mechanisms of DM prevention [13]. Increasing trunk fat represents a greater risk of hyperglycaemic status. A positive correlation between the hyperglycaemic status and the amount of abdominal adipose tissue was demonstrated in a study by Lin et al. [14]

A study by Chen et al. in 1350 Chinese nondiabetic adults focused on non-linear associations of BMI with HOMA indices, finding a positive association with IR but an inverse association with β-cell dysfunction [15]. In the present study, the same dependencies for BMI and both IR and β-cell dysfunction were revealed; however, we applied BMI as a linear adjustment on the indices relations to anthropometric variables.

The pathophysiology of IR is focused on 3 key tissues, namely skeletal muscle, liver, and adipose tissue. The regulation of insulinaemia is closely related to white adipocytes [16]. Our finding of HOMA-β increasing with growing BMI is consistent with the regulation mechanism. Obesity is also associated with mild chronic inflammation in target tissues, including adipose tissue. Immune cells may be the causal link between obesity and IR [17]. IR is considered to be a central abnormality linking a number of pathophysiological pathways, together resulting in DM and its complications. For example, high HOMA-IR levels are associated with decreased autonomic heart function and vagal activity, so IR prevention also reduces the risk of cardiac dysfunction [18]. DM is a recognized cause of accelerated aging,

and there is evidence that aging and DM share common pathophysiological pathways. The mechanisms linking advancing age to metabolic dysregulation are multifactorial and complex [8].

Published data from European countries show HOMA-IR values of around 2.0 to differentiate individuals with IR from the insulin sensitive [19]. In our study, the value of HOMA-IR in prediabetics was above this limit. IR can be present in young individuals without clinical manifestations, and it is possible to identify IR in time using HOMA-IR (values higher than 2.1) [20].

Recent studies have introduced new indices for the assessment of glycaemic variability and IR, which include in the calculation also BMI, high-density lipoprotein cholesterol, and triglycerides, all correlating with HOMA [21]. They point to the fact that, in addition to monitoring blood glucose levels, weight control remains the main tool for DM prevention. It is also necessary to determine how close people are to the cut-off point of metabolic syndrome (MetS) components [22]. Gesteiro et al. suggested using a clinical unit of pre-MetS allowing the establishment of public health policies to reduce the incidence of MetS. Defining a pre-MetS status might consider both emerging indicators (e.g. non-alcoholic liver fat disease or muscle strength) and variables already included in the definition of MetS [23].

In all subjects, HOMA indices were calculated based on the single measurements of blood glucose and insulin levels at a single time point. Suboptimal scattering of various ages in the study population did not enable the determination of a particular age of the maximum insulin secretion (the curve peak in Figure 3).

Conclusions

In a sample of obese individuals without DM, the mean values of HOMA-IR and HOMA-β in individuals with NGT were 1.5 and 82.8, respectively, while in prediabetics they were 2.2 and 74.3, respectively. HOMA values thus demonstrate the development of IR and at the same time the onset of β-cell dysfunction concerning the transition from NGT to prediabetes. The study confirmed a non-linear dependence of pancreatic β dysfunction, expressed by HOMA-β, on age but did not confirm this dependence in the case of HOMA-IR. Both indices were statistically significantly related to BMI, with a unit increase in BMI representing an increase in HOMA-IR by 0.1 and in HOMA-β by 3.2. BMI is thus a crucial factor in the development of peripheral IR as opposed to age. HOMA indices can reflect non-linear, closer-to-reality dependencies, which in many epidemiological studies are simplified to linear.

The assessment of glucose metabolism and IR using both HOMA indices is beneficial for the primary prevention of DM, given the relatively slow progression of the metabolic abnormalities, and should therefore be part of routine clinical practice. The results are valid for middle-aged European adults.

Learning points

— HOMA-IR, quantifying peripheral insulin resistance, depends on BMI, not on age;
— HOMA-β, determining insulin secretion, depends on BMI and quadratically on age;
— Both HOMA indices increase with BMI; HOMA-β decreases with age;
— HOMA can reflect non-linear, closer-to-reality dependencies;
— HOMA indices can help identify early metabolism disorders in clinical practice.

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