



## Tangled relationship between insulin resistance and microalbuminuria in children with obesity

Alberto Maria Colasante, Mario Bartiromo, Michele Nardolillo, Stefano Guarino, Pierluigi Marzuillo, Giuseppe Salvatore R C Mangoni di S Stefano, Emanuele Miraglia del Giudice, Anna Di Sessa

**Specialty type:** Pediatrics

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Geng TY, China; Liao Z, Singapore

**Received:** July 31, 2022

**Peer-review started:** July 31, 2022

**First decision:** September 5, 2022

**Revised:** September 19, 2022

**Accepted:** October 27, 2022

**Article in press:** October 27, 2022

**Published online:** November 9, 2022



Alberto Maria Colasante, Mario Bartiromo, Michele Nardolillo, Stefano Guarino, Pierluigi Marzuillo, Giuseppe Salvatore R C Mangoni di S Stefano, Emanuele Miraglia del Giudice, Anna Di Sessa, Department of Woman, Child, and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples 80138, Italy

**Corresponding author:** Anna Di Sessa, MD, PhD, Research Fellow, Department of Woman, Child, and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Via De Crecchio, Naples 80138, Italy. [anna.disessa@libero.it](mailto:anna.disessa@libero.it)

### Abstract

Childhood obesity represents a complex disease with a well-known cardio-metabolic burden including fatty liver, type 2 diabetes, metabolic syndrome, and cardiovascular disease. From a pathogenic point of view, insulin resistance (IR) represents the key factor underlying the spectrum of these obesity consequences. As observed in adults, recent data supported the occurrence of microalbuminuria (MA) as marker of early kidney dysfunction and its potential link with cardio-metabolic factors also in children with obesity. In fact, a well-documented pathophysiological hypothesis both in adults and children supported an intimate correlation with the major feature of obesity such as IR through the influence of insulin on renal hemodynamics. Based on the clinical and prognostic relevance of this relationship in daily practice (including an increased risk of chronic kidney disease development overtime), more scientific attention needs to be paid to the evaluation of early kidney damage in children with obesity. In this paper, we attempt to address three debated questions regarding the intriguing liaison between IR and MA in children with obesity: (1) What is the prevalence of pediatric MA? (2) What is the state of art of MA in children with obesity? and (3) Is there a link between IR and MA in children with obesity?

**Key Words:** Kidney damage; Microalbuminuria; Insulin resistance; Children; Obesity

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**Core Tip:** In addition to the well-known cardiometabolic consequences of obesity (including fatty liver, type 2 diabetes, metabolic syndrome, and cardiovascular disease), early kidney damage has been also demonstrated in children with obesity. As a consequence of the dysmetabolism, the occurrence of microalbuminuria as an early marker of kidney dysfunction has been widely described in these subjects and closely linked to insulin resistance. Given the lack of extensive pediatric data and the prognostic implications of this intriguing association, a better knowledge in this field is needed to counteract the intrinsic increased cardiometabolic risk of children with obesity.

**Citation:** Colasante AM, Bartiromo M, Nardolillo M, Guarino S, Marzuillo P, Mangoni di S Stefano GSRC, Miraglia del Giudice E, Di Sessa A. Tangled relationship between insulin resistance and microalbuminuria in children with obesity. *World J Clin Pediatr* 2022; 11(6): 455-462

**URL:** <https://www.wjgnet.com/2219-2808/full/v11/i6/455.htm>

**DOI:** <https://dx.doi.org/10.5409/wjcp.v11.i6.455>

## INTRODUCTION

Microalbuminuria (MA) has been largely recognized as an independent predictive and prognostic marker not only of renal dysfunction but also of cardiovascular morbidity and mortality[1-3] not only in adults with diabetes or obesity but also in healthy subjects[1]. MA is diagnosed when urinary albumin excretion (UAE) is 30-300 mg/24 h in a 24-h urine collection or 20-200 µg/min in a night time collection and ratio of urinary albumin to creatinine concentrations (UACR) is 30-300 mg/g or 3-30 mg/mmol in a first-morning urine sample random urine[2]. Estimates from cross-sectional studies found a prevalence of MA in healthy adult subjects of approximately 4%[3,4] (3.7% in males and 4.6% in females, respectively[4]) with a significant increase up to 6.2% in patients with obesity[4]. In particular, visceral obesity has been linked to MA, since the negative role of visceral adipose tissue on cardiovascular outcomes[5,6]. In this context, MA and obesity had a similar additive effect on the risk of death, independently of other common risk factors (*e.g.*, diabetes, smoking, hypertension)[7].

Owing to its clinical relevance as an early marker of glomerular damage preceding the onset of overt diabetic nephropathy by 10-14 years[8], MA prevalence has been studied also in adults with diabetes, ranging from 7.4% to 11.4%[3,4]. Given the beneficial influence of an optimal glycemic control on the entire spectrum of renal impairments diabetes-related (MA, nephropathy, micro- and macrovascular consequences), MA screening has been recommended in these subjects[9,10].

In contrast to robust evidence supporting the clinical significance of MA in morbid adults, pediatric data in this field are still very limited[1].

## WHAT ABOUT PEDIATRIC MA?

The evaluation of MA in healthy children and adolescents represents a pitfall since its potential relationship with strenuous exercise or febrile illness[11].

Based on cross-sectional data from NHANES III[2], MA prevalence in the first years of life has been found to be approximately 5.7%-7.3% in boys and 12.7%-15.1% in girls[1]. The higher percentage of MA in girls than boys could be attributed to the lower muscle mass and urinary creatinine excretion resulting in higher UACR values.

Remarkably, some studies reported an increased prevalence of MA in normal weight adolescents than in those with obesity[12-14]. Higher albumin excretion rate (ACR) levels have been significantly associated with a lower body mass index standard deviation score[15] and a higher height z-score[16]. In fact, healthy adolescents with MA are commonly thin and tall[16] and in these subjects MA might be directly related to the increased physical activity of thin children.

More, an increase of MA has been found in small for gestational-age children[1] and in school-age children[13]. In particular, the microalbumin/creatinine ratio in spot urine of healthy children decreased with increasing age[16]. A positive correlation between ACR and pubertal development stage has been also reported[17].

Of note, glucose metabolism impairments (*e.g.*, insulin resistance (IR)), pro-atherosclerotic pathways (*e.g.*, obesity), and haemodynamic load (*e.g.*, hypertension) have been largely accepted as the main cardiometabolic risk factors for the onset of MA in childhood[1,13,18].

Certain pathophysiological mechanisms such as low-grade inflammation, diffuse vascular damage with endothelial dysfunction[19], and increased permeability of the glomerular basement membrane[20] have been implied in urinary albumin loss.

## WHAT IS THE STATE OF ART OF MA IN CHILDREN WITH OBESITY?

Although there is a direct association between MA and metabolic syndrome in adults[21,22], no similar consensus has been currently reached in childhood[13,23,24]. As a consequence of pediatric obesity epidemic[21], MA has been described in these children but its relationship with metabolic milieu is still debating[25,26](Table 1).

In cross-sectional studies, MA prevalence in children and adolescents with obesity has been found to be approximately 6.4%[27]. Several clinical and cardiometabolic risk factors linked to MA in children and adolescents with obesity have been studied including age, sex, body mass index, waist circumference, triglycerides, high-density lipoprotein cholesterol, hypertension, and glycated hemoglobin (HbA1c)[28-30].

A large pediatric Korean study[23] demonstrated a significant association of MA with hyperglycemia [odds ratio (OR) 2.62, 95% confidence interval (CI): 1.09-6.30,  $P < 0.001$ ] in normal weight children, while hypertension (OR 14.10, 95%CI: 1.12-177.98,  $P < 0.001$ ) was found to be correlated to MA in children with obesity. Interestingly, HbA1c was associated with MA in both groups (OR 3.34, 95%CI: 1.09-10.17,  $P < 0.001$ , and OR 6.68, 95%CI: 1.87-23.95,  $P < 0.001$ , respectively)[21].

Nguyen *et al*[29] showed that overweight adolescents with impaired glucose tolerance, IR, and hypertension had MA, as previously demonstrated in adults[22,23]. From a pathogenic point of view, the increased intraglomerular capillary pressure consequent to the excess weight status might result in glomerular hyperfiltration. Consequently, it may potentially lead to MA through endothelial dysfunction triggered by specific “hits” as hypertension, impaired fasting glucose, diabetes mellitus, or smoking[31].

Lurbe *et al*[32] found that elevated urinary albumin excretion was correlated with higher waist circumference and insulin levels, by emphasizing the role of metabolic derangements in this relationship.

Cho and Kim[24] in a study on 1976 children and adolescents without diabetes mellitus, found a prevalence of MA in subjects with obesity of 3%. More, authors reported an association of HbA1c with MA regardless of weight status. In particular, a significant association of MA with hypertension was demonstrated in these patients, supporting the usefulness of MA as a marker of cardiovascular risk.

Another study[33] examined 105 pediatric patients with obesity divided into three groups as subjects with obesity only, subjects with obesity and metabolic syndrome, and subjects with obesity and type 2 diabetes. MA and increased levels of serum cystatin-C were found in patients with type 2 diabetes. In addition to glomerular damage IR-related, the tubule-interstitial injury might be further aggravated by glucose homeostasis dysregulation in patients with type 2 diabetes.

Burgert *et al*[34] reported a significant correlation of MA with post challenge alterations in glucose metabolism and insulin sensitivity loss in pediatric patients with obesity and normal glucose tolerance. In line with previous evidence[36], no association between metabolic syndrome and MA was reported, but results are affected by the lack of a control group.

Similarly, Bartz *et al*[35], in a study on 58 adolescents described an intriguing link between obesity-related IR (calculated through the euglycemic hyperinsulinemic clamp), and early MA onset. Indeed, insulin enhanced the effects of angiotensin II, contributing to hypertension, raised intraglomerular pressure, exacerbation of proteinuria, production of inflammatory cytokines, and apoptosis[36].

In contrast to the low prevalence of MA in the context of pediatric obesity reported in these studies, data on kidney function from adolescents with severe obesity reported a higher MA prevalence (17.3%)[37], suggesting a greater risk of chronic kidney disease for these patients.

In a study by Martin-Del-Campo *et al*[38] subjects with kidney alterations had higher body fat markers (including body mass index, waist circumference, fat percentage, subscapular skinfold, *etc.*) values and lower high-density lipoprotein cholesterol levels. Commonly, all these factors have been strongly associated with the development of kidney disease in adults[39-41]. In fact, fat deposition in the glomerulus may alter renal production of vasoactive and inflammatory mediators related to glomerular damages[42].

Also, in the study of Sanad and Gharib[43], MA was proposed as a marker of the endothelial dysfunction related to obesity and its metabolic consequences. Indeed, a positive correlation between MA and a worse cardiometabolic profile (including abdominal obesity, dyslipidemia, hypertension, IR, and impaired glucose tolerance) was demonstrated in children with obesity.

Similar evidence was provided by Savino *et al*[44]. Although no clinical evidence of kidney dysfunction was found in youths with obesity compared to healthy controls, MA was confirmed to be associated with hypertension, adiposity, and IR.

Csernus *et al*[45], found that children with obesity and glucose homeostasis abnormalities (including hyperinsulinemia and impaired glucose tolerance) and had a higher urinary albumin/creatinine ratio than normal weight children, supporting the central role of these factors in the development of kidney damage.

On the other hand, there is some contrasting evidence[29] reporting no association between MA and cardiometabolic risk factors in childhood obesity. To explain this, it could be supposed that a longer dysmetabolism (including duration of obesity and IR status) is required for renal dysfunction development.

**Table 1 Main studies on microalbuminuria in children with obesity**

Ref.	Study design	Population	Main findings
Savino <i>et al</i> [44]	Case Control	One hundred seven OB Caucasian prepubertal and pubertal children and adolescents of both sexes (M 52, F 55). Fifty normal weight Caucasian children as control group (M 26, F 24)	A modest significant difference was seen in AER values, which were higher in the OB group, even if mostly within normal range. AER showed a positive correlation with central adiposity, insulin resistance indexes and hypertension
Sanad and Gharib[43]	Cross – Sectional	One hundred fifty prepubertal obese children. Exclusion criteria: fever, infections, renal diseases, LES, endocrine disorders, albuminuria associated with urinary tract infections	There were significant positive correlations between MA and BMI, WC, systolic and diastolic BP, TG and LDL-c levels, insulin resistance and fasting glucose level. In contrast, there was a negative correlation between MA and HDL-c levels ( $P < 0.01$ ). No significant correlations of MA with age and sex were found ( $P > 0.05$ )
Csernus <i>et al</i> [45]	Case-Control	Eighty-six obese children. Seventy-nine normal weight children as a control group. children with secondary obesity were excluded	OB children with obesity had a significantly higher U-ACR and U-BMCR as compared to the normal weight children. OB children with no more than one of cardiovascular risk factors ( <i>e.g.</i> , hyperinsulinemia, fasting or post-prandial glucose, dyslipidemia and hypertension) had a significantly lower U-ACR than those with two or more features. U-ACR was positively correlated with body weight and with the fasting plasma glucose concentrations measured during the OGTT. U-ACR was increased in OB children with hypercholesterolemia. No association of U-ACR with TG and HDL-c levels was found
Goknar <i>et al</i> [30]	Case-Control	Eighty-four OB individuals aged 4-16 yr as study (case) group. Sixty-four normotensive healthy children as control group	No statistically significant differences were found in urine microalbumin/creatinine ( $P = 0.740$ )
Hirschler <i>et al</i> [12]	Retrospective Study	One thousand five hundred sixty-four children aged 5-14 yr, 220/1564 OB (14.1%), 300/1564 OW (19.2%), 1044/1564 (66.7%) normal weight, 318/1564 (20.3%) central OB	U-ACR decreased with increasing z-BMI for boys and girls. Median ACR and urinary albumin levels were significantly higher in normal weight children than in OW/OB children. Median ACR and urinary albumin levels was higher in OB girls than in OB boys
Radhakishun <i>et al</i> [28]	Retrospective	Four hundred eight OB children aged 3-19 yr, 50 % males	A low prevalence of MA (2.7%) was found. All subjects with MA were obese
Oz-Sig <i>et al</i> [33]	Retrospective	One hundred and five obese children (M 39) aged 4-18 yr. The cohort was divided into three groups as solely obese, with metabolic syndrome and with type 2 diabetes. MA was tested in 24 h collected urine (MA: 30-300 mg)	MA was significantly higher in type 2 diabetic group; statistical significance was reached in the group with metabolic syndrome and type 2 diabetic group. MA was not detected in the solely obese group
Lurbe <i>et al</i> [32]	Retrospective	One hundred and thirty-four OB children aged 9-18 yr. Obesity: z score $> 2$ , Moderate obesity: z score 2-2.5. Severe obesity: z score $> 2.5$ . UAE was measured in the first voiding urine of the morning	No differences between different groups of obesity degree were found. Increased UAE was linked to fasting Insulin HOMA Index, higher WC, and TG levels
Cho <i>et al</i> [15]	Retrospective	One thousand four hundred and fifty-nine adolescents aged 12-18 yr	MA was detected in 3.6% of subjects (53/1459). The Height z score of the MA group was greater than that of the NA group. The Weight z score of the MA group did not differ from that of NA group. The MA group had a lower BMI z score. MA group had higher HDL-c and lower TG levels. No significant differences in BP, fasting glucose, total cholesterol, and LDL levels were reported. UACR was associated with younger age, lower weight z score, lower BMI z score, lower W/Hr, but not with the height z score. UACR was associated with higher HDL level and lower TG values
Burgert <i>et al</i> [34]	Cohort Study	Two hundred seventy-seven children and adolescents	MA was found in 10.1 % of subjects (28/277). No significant differences between the two groups (MA e NA) in term of the anthropometrical and common cardiovascular risk factors were reported. Subjects with MA had higher plasma glucose and insulin levels during OGTT
Nguyen <i>et al</i> [29]	Cross Sectional	Two thousand five hundred fifteen adolescents aged 12-19 yr. 310/2515 children with BMI $> 95$ pc.	MA was detected in 8.9% of the study population. UACR girls was significantly higher in girls than in boys. MA was prevalent among NON-OW adolescents. Similarly, MA was prevalent among adolescents without abdominal obesity, and without insulin resistance
Martin-Del-Campo <i>et al</i> [38]	Cross Sectional	One hundred seventy-two children and adolescents aged 6-16 yr, 46/172 (27%) normal weight, 55/172 (32%) overweight, 71/172 (41%) obesity	MA was observed in children with OW (3.6%) and with OB (9.9%) more than in normal weight children

AER: Albumin excretion rate; BMI: Body mass index; HDL-c: High-density lipoprotein- cholesterol; LDL-c: Low-density lipoprotein- cholesterol; MA: Microalbuminuria; NA: Normal albuminuria; OB: obese; OGTT: Oral glucose tolerance test; OW: overweight; TG: Triglycerides; U-ACR: Urinary albumin/creatinine ratio; UAE: Urinary albumin excretion; U-BMCR: Urinary beta-2-microglobulin/creatinine ratio; WC: Waist circumference; W/Hr: waist-to-height ratio.

An Italian study[46] involved 901 children and adolescents subdivided according to estimated glomerular filtration (eGFR). Children with mild-low eGFR (< 20<sup>th</sup> percentile) and high eGFR (> 80<sup>th</sup> percentile) had an increased presence of cardio-metabolic risk factor. Between these, children with reduced eGFR levels had a worse cardio-metabolic profile. Considering this, authors suggested eGFR as a useful tool to identify children at greater cardiometabolic risk.

Similar findings were reported in another cross-sectional study examining 360 children with obesity [28]. Subjects with eGFR > 1 SD had higher systolic blood pressure, glucose, and insulin levels in response to oral glucose tolerance test. No significant association was demonstrated between MA (reported in 6.4% of subjects) and other cardiometabolic markers in children with obesity, although a lower insulinogenic index in subjects with MA was reported.

## IR AND MA IN CHILDHOOD OBESITY: IS THERE A LINK?

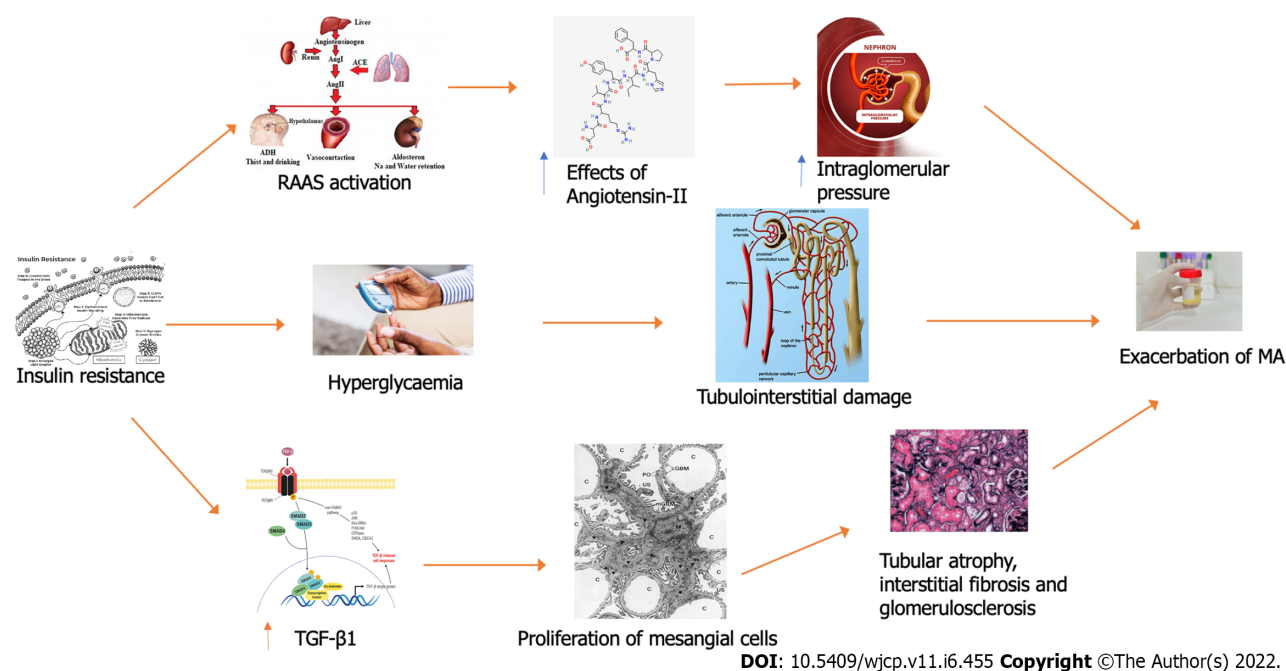
As observed adults[7,39], early renal damage (expressed as MA) has been demonstrated as a consequence of obesity in childhood[1,12,26]. Robust evidence has shown that MA represents a close reflection of the systemic vascular endothelial damage status[26,34,35]. In this tangled framework, a pivotal pathogenic role in the development of the underlying renal hemodynamic abnormalities has been widely recognized for IR[26,32,35] (Figure 1). As a consequence of a reduced insulin sensitivity, hyperinsulinemia- through the well-documented conflicting effects of insulin (both antinatriuretic and at tubular and glomerular level, respectively), acts as a key player in the tangled dysregulation of renal hemodynamics (including glomerular hyperperfusion, hyperfiltration, *etc.*) occurring in children with obesity[47,48]. To complicate matter, IR seems to mediate the intertwined relationship of MA with obesity and early renal impairment[35]. Classically, several different signaling pathways are involved in IR development and have been found to act also in the early stages of renal injury[26,34,35]. Therefore, MA represents an early predictive cardiometabolic risk marker as its close relationship with endothelial dysfunction reflecting both renal and systemic endovascular damage[26,34,35]. Although the current paucity of data examining the association of IR with MA in children with obesity, there is some pediatric evidence linking this latter to cardiometabolic risk factors[23,25,26,43]. IR represents a central player in Metabolic syndrome, in turn closely related to obesity, realizing a dangerous vicious circle[26,43,46]. In particular, the adiposity-related IR might lead to endothelial dysfunction with subsequent increased permeability responsible for the loss of albumin and other molecules involved in lipid accumulation and inflammation in the wall of vessels[26,43]. Taken together, these derangements might represent a potential pathophysiological explanation of kidney damage observed in children with obesity[26,43,47].

As the relevant prognostic implications of the relationship between MA and IR on the cardio-metabolic burden of children with obesity[49], this intriguing link deserves to be further strengthen in larger pediatric studies.

## CONCLUSION

Within the spectrum of the pediatric obesity-related consequences, recent data have focused on the risk of early kidney damage in these children. Although still contrasting, a large body of evidence supported a complex relationship of MA with IR. Noteworthy, this latter represents an intriguing shared risk factor between obesity and early renal impairment.

Taking into account the adverse prognostic implications of the association of MA with IR not only on renal function but also on the general health status of children with obesity, we believe that MA evaluation should be included in the overall assessment of these patients as subjects with an intrinsic higher cardiometabolic risk.



**Figure 1 Pathophysiological link between microalbuminuria and insulin resistance.** MA: Microalbuminuria; TGF- $\beta$ 1: Transforming growth factor- $\beta$ 1; RAAS: Renin-angiotensin-aldosterone system.

## FOOTNOTES

**Author contributions:** Colasante AM and Di Sessa A wrote the manuscript; Miraglia del Giudice E, Di Sessa A and Marzuillo P conceived the manuscript; Miraglia del Giudice E, Di Sessa A, and Marzuillo P supervised the manuscript drafting; Nardolillo M, Bartiromo M, Guarino S and Mangoni di S Stefano GSRC reviewed the literature data; Colasante AM and Nardolillo M prepared the table and the figure; each author contributed important intellectual content during manuscript drafting or revision.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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**Country/Territory of origin:** Italy

**ORCID number:** Alberto Maria Colasante 0000-0001-6346-9787; Mario Bartiromo 0000-0002-5958-3314; Michele Nardolillo 0000-0002-1608-4777; Stefano Guarino 0000-0002-0551-5236; Pierluigi Marzuillo 0000-0003-4682-0170; Emanuele Miraglia del Giudice 0000-0002-1492-076X; Anna Di Sessa 0000-0002-5877-3757.

**S-Editor:** Gao CC

**L-Editor:** A

**P-Editor:** Zhang XD

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