

# Intra-abdominal hypertension and increased acute kidney injury risk: a systematic review and meta-analysis

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## Abstract

**Objective:** The present meta-analysis aimed to determine the relationship between intra-abdominal hypertension (IAH) and an increased prevalence of acute kidney injury (AKI) and identify the associated risk factors in various patient populations, regardless of whether they were admitted to an intensive care unit.

**Methods:** We used three databases for the following search terms: “IAH,” “abdominal compartment syndrome,” “AKI,” “acute kidney failure,” and others. The articles retrieved were compared to identify appropriate studies published until 7 May 2020. The main outcome was AKI.

**Results:** Six studies with 344 individuals were included. The patients were divided into two main groups: the IAH and non-IAH groups. Compared with patients without IAH, patients with IAH had a higher risk of AKI (odds ratio = 2.57, 95% confidence interval: 1.55–4.26). In the subgroup and meta-regression analyses, body mass index, age, the presence or absence of burns, and cardiac surgery did not affect the risk of AKI.

**Conclusion:** IAH was associated with AKI risk, and this association was not influenced by age, body mass index, the presence or absence of burns, or cardiac surgery.

## Keywords

Intra-abdominal hypertension, intra-abdominal pressure, acute kidney injury, meta-analysis, abdominal compartment syndrome, intensive care unit

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## Introduction

Intra-abdominal pressure (IAP) is an important clinical variable in critically ill patients after surgery.<sup>1</sup> Intra-abdominal hypertension (IAH) is defined as an IAP  $\geq 12$  mmHg according to the World Society of Abdominal Compartment Syndrome (WSACS).<sup>2</sup> An IAP of 20 mmHg is associated with abdominal compartment syndrome (ACS), which can lead to the failure of multiple organs, including the kidneys and lungs.<sup>3,4</sup> However, the significance of IAH is often underappreciated by clinicians.<sup>3,5</sup> A clinical survey indicated that less than 30% of doctors were aware of the definition of IAH, and only a few of them understood how to apply the WSACS guidelines for patients with increased IAP.<sup>5</sup>

A recent worldwide cohort study of 15 intensive care units (ICUs) that screened 491 patients found that IAH was present in 34% of patients on the day of ICU admission, and nearly 50% of individuals developed IAH during the observational period. This study also found that IAP was increased in almost 50% of all patients in ICUs, and the severity of IAP was found to independently increase the 28- and 90-day mortality rates.<sup>6</sup> Indeed, a large number of patients with IAH develop organ failure, a complication that occurs even with moderate increases in IAP.<sup>7</sup> For instance, higher levels of necrosis in the gut mucosa and respiratory diseases have been found among patients with IAH.<sup>4,8</sup> Acute kidney injury (AKI) is gradually being recognized as a complication of IAH. Although the mechanism of IAH-induced AKI remains unclear, three main factors are suspected to be involved: (1) isolated elevation in renal vein pressure,<sup>9</sup> (2) increased renal parenchymal pressure indirectly causing renal dysfunction via ischemic insult,<sup>10</sup> and (3) elevation in catecholamine, renin, angiotensin, and

inflammatory cytokine levels.<sup>11–13</sup> However, another study reported that IAH did not predict the risk of AKI.<sup>14</sup> Moreover, other events in critically ill patients may worsen renal perfusion, such as severe infection.

Thus, it remains unclear whether IAH increases the risk of AKI. Therefore, the present meta-analysis aimed to comprehensively summarize the available data on the relationship between increased IAP and the risk of AKI to raise the awareness of IAH and IAH-induced AKI among physicians and facilitate their timely detection and treatment.

## Materials and methods

### Literature search

The present systematic review and meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>15</sup> The PubMed, Cochrane Library, and EMBASE databases were searched to identify appropriate studies published until 7 May 2020. A combination of free terms and Medical Subject Heading terms was used to select the following search terms: (intra-abdominal pressure OR intra-abdominal hypertension OR abdominal compartment syndrome) and (acute kidney disease OR kidney diseases OR renal insufficiency OR acute kidney injury OR acute kidney failure OR AKI OR AKF). Ethical approval and informed consent were not applicable because this study was a meta-analysis of published data.

### Study selection

Two reviewers independently selected relevant studies based on the selection criteria. Studies were included in this meta-analysis if they met the following criteria: (a)

individuals with IAH, (b) IAH definition based on the WSACS recommendations, (c) acute kidney disease, and (d) observational studies. Studies were excluded if the participants had acute kidney disease before admission or if all participants were under 18 years of age. Duplicated articles were removed using the Endnote X9 software package (Clarivate, Philadelphia, PA, USA), and potentially eligible studies were identified by screening the titles and abstracts of the remaining articles. The full texts of the studies were subjected to a thorough review to identify appropriate trials for inclusion in this meta-analysis. Any disagreements were resolved by consultation with a third reviewer. If the odds ratio (OR) for IAH and AKI was provided in a particular study, we used the value directly. If not, we used Review Manager (RevMan) [computer program] Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to calculate the OR for the IAH group vs. the non-IAH group.

### Quality assessment

The Newcastle–Ottawa Scale was used to determine the quality of the included trials. Two reviewers independently graded the included trials according to the following categories: ascertainment of outcomes, comparability of study groups, and selection of participants. The items in the above categories were awarded a maximum of four stars, and studies with 7 to 9 stars were deemed to be of high quality.

### Statistical analysis

All statistical analyses were conducted using the STATA software package version 11.0 (Stata Corp., College Station, TX, USA). We compared the risk of AKI between the IAH and non-IAH groups. The results were expressed as combined

ORs. When the  $I^2$  statistic was  $<50\%$ , a fixed-effects model was applied; otherwise, a random-effects model was used. Visual inspection of funnel plots was used to detect publication bias. Funnel plot asymmetry was assessed using the Egger test and Begg test ( $P < 0.1$ ).  $P$  values less than 0.05 were considered statistically significant.

## Results

### Characteristics of included studies

Of 359 screened studies, 6 were included in this meta-analysis (Figure 1). These six studies enrolled a total of 344 patients, including patients admitted to an ICU and patients receiving tertiary care. Most patients were European. The main characteristics and quality of the six included studies are shown in Tables 1 and 2, respectively.

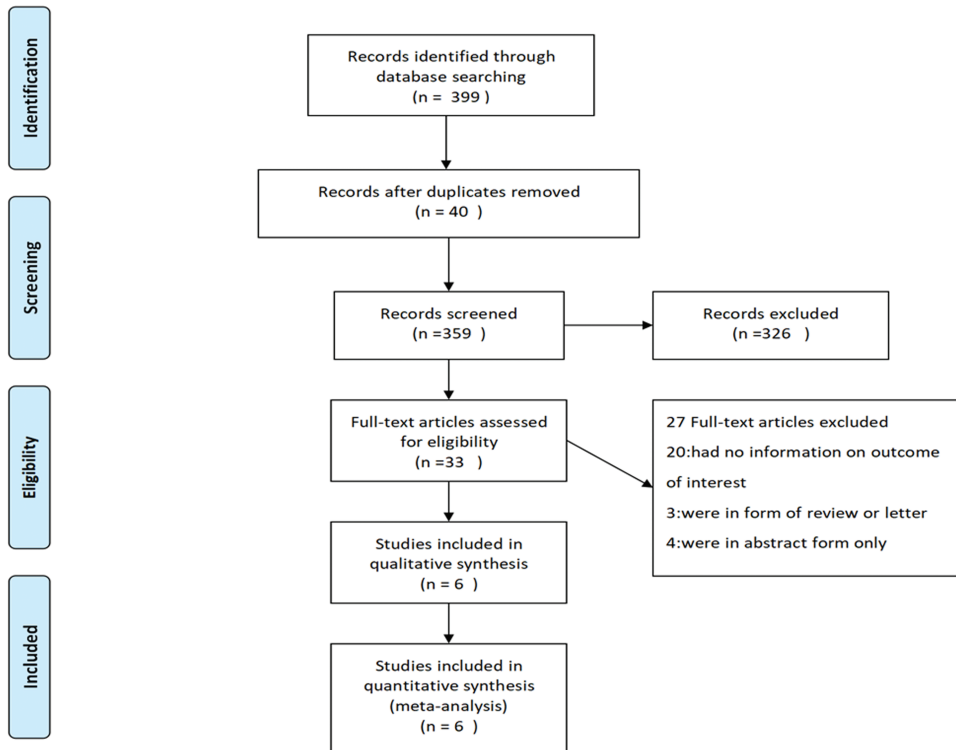
All included studies compared the IAH group with the non-IAH group. ORs were used in all studies. AKI was not present at the time of admission in any of the patients.

### IAH group vs. non-IAH group

Compared with the non-IAH group, the IAH group showed a higher incidence of AKI (Figure 2), as determined using the fixed-effects model [ $I^2 = 4.48$ , OR = 2.57, 95% confidence interval (CI): 1.55–4.26,  $P < 0.001$ ]. No significant heterogeneity was present.

### Subgroup and meta-regression analysis

We conducted a subgroup analysis by dividing individuals into several groups based on the cause of hospital admission, whether or not they had undergone cardiac surgery, average age, and body mass index (BMI). The subgroup analysis indicated that IAH increased the risk of AKI regardless of the average age compared with patients without IAH ( $\geq 60$  years:



**Figure 1.** PRISMA flowchart of study selection

OR = 2.56, 95% CI: 1.16–5.63,  $P=0.02$ ; <60 years: OR = 2.57, 95% CI: 1.33–4.98,  $P=0.005$ ). The incidence of a BMI  $\geq 24$  significantly differed between the IAH and non-IAH groups (OR = 4.26, 95% CI: 1.42–12.78,  $P=0.01$ ; Figure 3). However, in the meta-regression models based on patient characteristics, BMI and average age were not associated with the risk of AKI. In addition, the presence or absence of burns or cardiac surgery did not affect the risk of AKI (Table 3).

#### *Publication bias and sensitivity analysis*

No significant funnel plot asymmetry (Figure 4) or publication bias was found. Sensitivity analysis could not be conducted owing to the limited number of trials.

## **Discussion**

IAH is frequently linked to ACS,<sup>16</sup> which contributes to serial organ dysfunction. However, the impact of IAH is underestimated and remains controversial.<sup>3</sup> This meta-analysis is the first to demonstrate that acute renal outcomes were linked to IAH in patients in ICUs and not in ICUs. In addition, we demonstrated that patient characteristics, such as age, BMI, the presence or absence of burns, or cardiac surgery, were not linked to the risk of IAH-induced AKI.

An increasing number of studies are now reporting that IAH may lead to AKI. Demarchi et al. reported that increased IAP was related to a higher incidence of AKI after abdominal surgery; the authors found that the IAP measured on the day of

**Table 1.** Characteristics of observational trials included in the meta-analysis

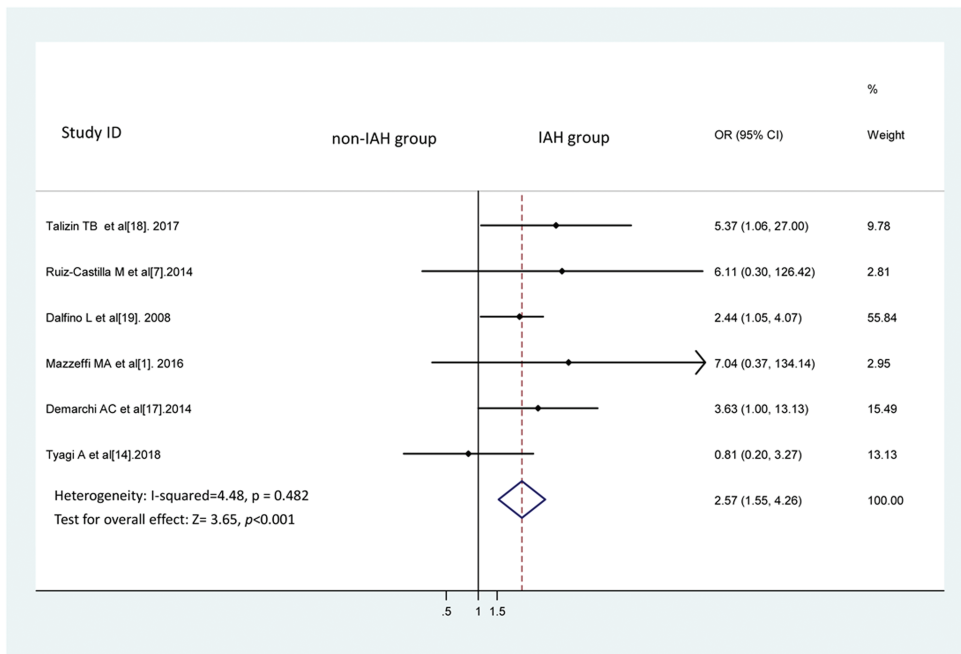
Study	Country	Men/ Patients (n/n)	BMI (kg/m <sup>2</sup> )	Mean age (yrs)	Baseline comorbidities and ward/room	Mean IAP	How and when IAP was measured	IAH definition	Concomitant treatment	Outcome	Outcome definition
Talizin et al. <sup>18</sup> , 2017	Brazil	33/46	NR	41	Burns; in an ICU room	15.0 mmHg	Measurement was within 3 hours of admission; the AbViser measurement system was used.	≥12 mm Hg	Vasopressors, mechanical venti- lation, glycopepti- des, polymyxin	AKI	KDIGO (2012)
Ruiz-Castilla et al. <sup>7</sup> , 2014	Spain	21/25	24.5	42	Cancer, hypertension, ische- mic cardiopathy; in the Burns Unit	13 mmHg	Measurement was every 6 hours during the 5-day study period; a closed measurement system (Abdo-Pressure™, ConvatecSL, Espana) was used.	≥12 mm Hg	Mechanical ventila- tion, crystalloids	Renal failure	Plasma creatinine >1.5 mg/dL during first 5 days of admission
Dalfino et al. <sup>19</sup> , 2008	Turkey	78/123	NR	62	Chronic cardiovascular dis- ease, chronic respiratory disease, chronic renal dis- ease, chronic liver disease; in a mixed ICU room.	12 mmHg	Measurements were performed on admission and at least every 24 hours; a Foley blad- der catheter was used.	≥12 mm Hg	Diuretics, CRRT, crystalloids	RIFLE	ADQI (2004)
Mazzeffi et al. <sup>1</sup> , 2016	USA	29/42	29.1 ±5.2	61	Chronic lung disease, periph- eral vascular disease, cerebrovascular disease; in the general ward	NR	Measurements were prior to surgery; immediately after surgery in the operating room; and 3, 6, 12, and 24 hours after surgery; bladder pressure was used.	≥12 mm Hg	NR	RIFLE	ADQI (2004)
Demarchi et al. <sup>17</sup> , 2014	USA	35/60	26 ± 5.0	59	NR; in an ICU room	NR	Measurements were at admission to the ICU; bladder pressure was used.	≥12 mm Hg	NR	AKI	KDIGO (2012)
Tyagi et al. <sup>14</sup> , 2018	India	0/48	22.2 ± 3	25	NR; in an ICU room	NR	Measurements were twice daily; a Foley bladder catheter was used.	≥12 mm Hg	NR	AKI	KDIGO (2012)

BMI, body mass index; IAP, intra-abdominal hypertension; ICU, intensive care unit; AKI, acute kidney injury; NR, not reported; KDIGO, Kidney Disease Improving Global Outcomes; ADQI, Acute Dialysis Quality Initiative; RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease.

**Table 2.** Newcastle–Ottawa Scale quality assessment of included studies.

	Selection of participants	Comparability of study groups	Assessment of outcome/ascertainment of exposure	Total score*
Talizin et al. <sup>18</sup>	<★★★★>	<★★★>	<★★★>	7
Ruiz-Castilla et al. <sup>7</sup>	<★★★★>	<★★★>	<★★★>	7
Dalfino et al. <sup>19</sup>	<★★★★★>	<★★★>	<★★★>	8
Mazzeffi et al. <sup>1</sup>	<★★★★>	<★★★>	<★★★>	7
Demarchi et al. <sup>17</sup>	<★★★★>	<★★★>	<★★★>	7
Tyagi et al. <sup>14</sup>	<★★★★>	<★★★>	<★★★>	7

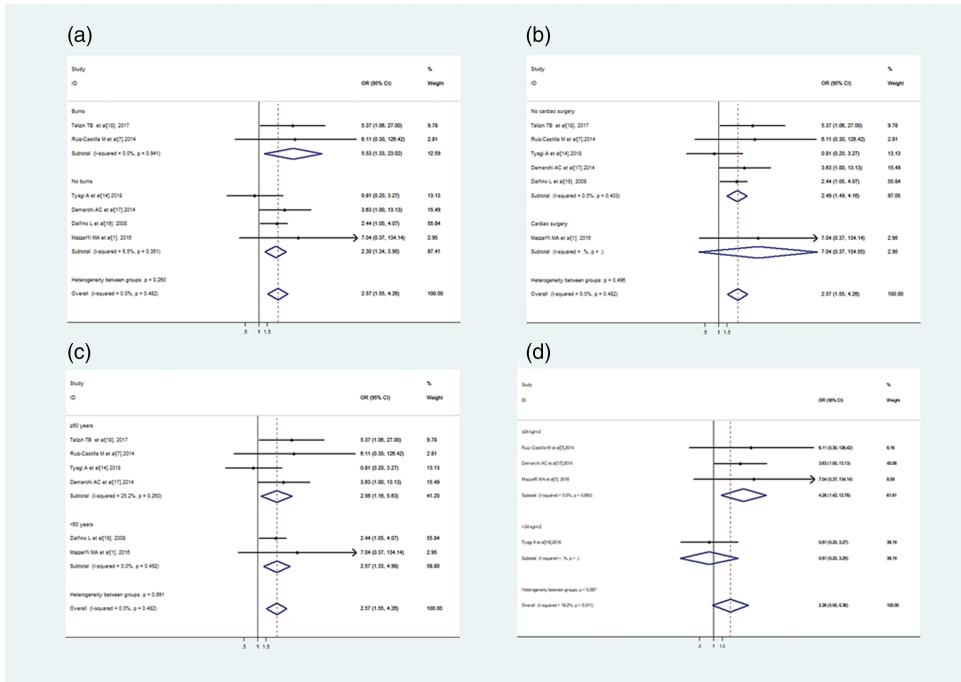
\*Studies with 7 to 9 stars were deemed to be of high quality.



**Figure 2.** IAH and the risk of AKI. We compared the risk of AKI between the IAH and non-IAH groups using a fixed-effects model. The results were expressed as combined ORs. IAH, intra-abdominal hypertension; AKI, acute kidney injury; OR, odds ratio; CI, confidence interval.

ICU admission significantly predicted the development of AKI in this population with a sensitivity of 87% and a specificity of 46%. In addition, IAH does not always occur after surgery.<sup>17</sup> Mazzeffi et al. reported that among 42 patients undergoing cardiac surgery, 35 (83.3%) patients had at least one elevated IAP measurement

during the perioperative period; the authors concluded that in patients undergoing cardiac surgery, IAH might increase the risk of AKI, which is consistent with our results. The above findings indicate that AKI might be related to IAH, regardless of the severity of illness and the operation type.<sup>1</sup> However, one study reported that IAP did not



**Figure 3.** Subgroup analyses. Burns and No burns (a), Cardiac surgery and No cardiac surgery (b), and average age  $\geq 60$  years and average age  $< 60$  years between the IAH group and Non-IAH group (c). Subgroup analysis of BMI  $\geq 24$  kg/m<sup>2</sup> and BMI  $< 24$  kg/m<sup>2</sup>. IAH, intra-abdominal hypertension; BMI, body mass index; OR, odds ratio; CI, confidence interval.

**Table 3.** Subgroup analysis and meta-regression models

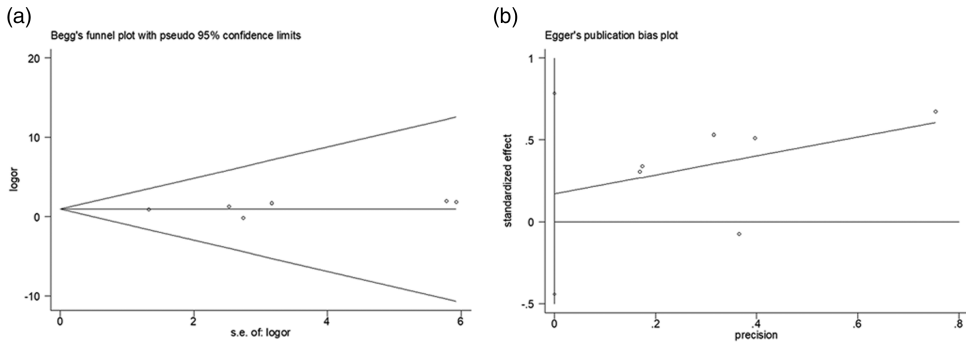
Subgroup	Studies (n)	P value*	P value**
<b>Cause of hospital admission</b>			
Burns	2	0.019	0.32
No burns	4	0.003	
Cardiac surgery	1	NA	0.53
No cardiac surgery	5	0.194	
<b>Average age</b>			
IAH vs. Non-IAH			
$\geq 60$ years	4	0.02	0.96
$< 60$ years	2	0.005	
<b>Body mass index</b>			
$\geq 24$ kg/m <sup>2</sup>	3	0.01	0.21
$< 24$ kg/m <sup>2</sup>	1	NA	

IAH, intra-abdominal hypertension.

\*P value represents test effect of subgroup analysis; \*\*P value represents interaction assessed by meta-regression models.

correlate with early AKI in critically ill obstetric patients.<sup>14</sup> Therefore, we conducted a meta-analysis and determined the following: (1) IAH was associated with a higher prevalence of AKI; (2) the pooled OR demonstrated a 2.57-fold increased risk of AKI; and (3) our meta-analysis included both burn and non-burn patients, patients who underwent cardiac surgery and those who underwent non-cardiac surgery,<sup>1,7,18,19</sup> patients whose average age was  $\geq 60$  years and those whose average age was  $< 60$  years, and patients whose BMI was  $\geq 24$  kg/m<sup>2</sup> and those whose BMI was  $< 24$  kg/m<sup>2</sup>. Nevertheless, there was no heterogeneity among the included studies.

Persistent IAH is theorized to lead to a higher incidence of AKI via three main mechanisms. First, the IAH-induced



**Figure 4.** Egger test (a) and Begg test (b) results of the 6 included studies. Visual inspection of funnel plots was performed to detect publication bias. Funnel plot asymmetry was assessed using the Egger test and Begg test ( $P < 0.1$ )

decrease in renal function may be a consequence of increased renal vein pressure. One study of a swine model reported that an elevation in renal vein pressure (0–30 mmHg above the baseline) in the experimental group resulted in a significant decrease in the glomerular filtration rate (from 26 mL/min to 8 mL/min) compared with the control group.<sup>9</sup> These changes were partially or completely reversed by decreasing the renal vein pressure. Second, the elevation in renal parenchymal pressure in a porcine model was not associated with a significant change in the glomerular filtration rate compared with the control group;<sup>20</sup> nevertheless, elevated renal parenchymal pressure might indirectly cause renal dysfunction via renal ischemia.

There are other factors in the included studies that may be responsible for AKI, such as mechanical ventilation (MV). A systematic review and meta-analysis showed that invasive MV is associated with a three-fold increase in the likelihood of developing AKI, and various tidal volume and positive end-expiratory pressure settings do not modify this risk.<sup>21</sup> Of the six articles included in this study, four articles found no link between MV and AKI,<sup>7,14,17</sup> and two articles provided no data regarding

MV causing AKI.<sup>1,19</sup> Only one study indicated a link between MV and AKI.<sup>18</sup> Therefore, in the present study, we consider that the influence of MV was negligible.

Certain limitations of our study must be acknowledged. First, few clinical trials were included, and all had relatively small sample sizes. Second, the study design was not blinded, and the effect of confounding factors cannot be excluded. Third, the outcome definitions were different. In the future, large-scale studies involving a stratified analysis of the association between IAH and AKI are required.

## Conclusion

The present meta-analysis found that IAH was linked to a higher prevalence of AKI. In addition, patient characteristics, such as burns, cardiac surgery, age, and BMI, did not influence the risk of IAH-induced AKI. Further trials are needed to verify the relationship between IAH and AKI in different populations and determine how IAH-induced AKI may be prevented.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.



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