Visceral adiposity and colorectal adenomas: dose-response meta-analysis of observational studies

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Background: Obesity-related hormonal and metabolic perturbations implicated in colorectal carcinogenesis are mainly driven by visceral adipose tissue (VAT) rather than subcutaneous adipose tissue (SAT). Yet, most epidemiologic studies have examined the relationship between excess adiposity and colorectal neoplasia using body mass index (BMI) and waist circumference (WC). Due to the inability of BMI and WC to distinguish VAT from SAT, they are likely to have underestimated the true association.

Patients and methods: We conducted a dose–response meta-analysis to summarize the relationships between VAT and colorectal adenomas and to examine the value of VAT as an independent risk factor beyond BMI, WC, and SAT. PubMed and Embase were searched through September 2014 to identify relevant observational studies. The summary odds ratio (OR) 95% confidence interval (CI) were estimated using a random-effects model.

Results: In linear dose–response meta-analysis, the summary OR for each 25 cm² increase in VAT area was 1.13 (95% CI 1.05–1.21; I² = 62%); 6 studies; 2776 cases; range of VAT area = 30–228 cm²). The dose–response curve suggested no evidence of nonlinearity (P non-linearity = 0.37). In meta-analysis comparing the highest versus lowest category of VAT based on 12 studies, a positive association between VAT and adenomas remained statistically significant even after adjustment for BMI, WC, and SAT. In contrast, adjustment for VAT substantially attenuated associations of BMI, WC, and SAT with adenomas. Across the studies, VAT was more strongly associated with advanced adenomas than nonadvanced adenomas.

Conclusions: VAT may be the underlying mediator of the observed associations of BMI and WC with adenomas, increasing adenoma risk continuously over a wide range of VAT area. Considering that the joint use of BMI and WC better captures VAT than the use of either one, clinicians are recommended to use both BMI and WC to identify those at high risk for colorectal neoplasia.

Key words: visceral adiposity, visceral adipose tissue, colorectal adenomas, dose–response meta-analysis, observational studies

Introduction

Adipose tissue, once regarded as a simple reservoir of excess calories, is now recognized as an active endocrine and metabolic organ. Excess adiposity results in an elevation in circulating concentrations of insulin and bioavailable IGF-I [1], which promotes colorectal carcinogenesis by enhancing proliferation and inhibiting apoptosis of colonocytes [2]. Epidemiologic studies have shown that the amount (i.e. overall adiposity) and distribution (i.e. abdominal obesity) of excess adiposity as assessed by body mass index (BMI) and waist circumference (WC), respectively, are independent risk factors of colorectal neoplasia [3].
Yet, emerging evidence suggests the importance of distinguishing visceral adipose tissue (VAT) surrounding the internal organs from subcutaneous adipose tissue (SAT) located beneath the skin, above and beyond the amount and distribution of adipose tissue [4].

SAT and VAT have different metabolic consequences. Relative to SAT, VAT is more strongly associated with insulin resistance. VAT secretes more proinflammatory cytokines (e.g. interleukin-6, tumor necrosis factor-α) and less adiponectin, which contributes to insulin resistance [4, 5]. Furthermore, VAT is more hypolipidic, effusing free fatty acids into the circulation [6]. To regulate the rise in plasma free fatty acids levels, the liver and muscle become less responsive to insulin (i.e. insulin resistance), preferentially uptaking and oxidizing fatty acids over glucose [1, 6]. The hyperinsulinemia resulting from insulin resistance suppresses hepatic production of hormonal binding proteins (e.g. IGF binding protein), which in turn increases bioavailability of IGF-1 [1]. Due to the critical role of VAT in elevating circulating levels of insulin and bioavailable IGF-1, it has been hypothesized that observed associations of BMI and WC with colorectal neoplasia may be mainly mediated by VAT. Indeed, in a study that compared various indices of adiposity including SAT, VAT, total abdominal adipose tissue (SAT + VAT), BMI, and WC, only VAT was a statistically significant determinant of colorectal neoplasia [7].

Despite the biological plausibility supporting the specific deleterious effect of VAT on colorectal neoplasia, as the direct measurement of VAT requires costly medical equipment such as computed tomography (CT) or magnetic resonance imaging (MRI), only a few studies have investigated the relationship between VAT and colorectal neoplasia. Furthermore, available studies are of small size, cross-sectional or case–control design, and with adenoma outcome (a precursor lesion that can progress to colorectal cancer) and inconclusive individually. To examine the relationship between VAT and adenomas with improved precision, we conducted a meta-analysis, with a particular focus on if VAT has an independent effect above beyond other adiposity indices. Given that there is no standardized guideline defining normal amount of VAT, we conducted dose–response meta-analyses to identify the shape of the relationship and quantify the risk associated with an increase in VAT.

methods

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist [8] was followed for the design, analysis, and reporting of this meta-analysis. Two authors (DL and RK) participated in literature search, study selection, and data extraction independently. Inconsistency between researchers was resolved through discussion with a third author (NK).

literature search

PubMed and Embase databases were searched for studies published up to September 2014. Detailed search terms are provided (supplementary Table S1, available at Annals of Oncology online). The language was limited to English and no other restrictions were imposed. Abstracts and unpublished results were not included. The reference lists of all the articles included in this analysis were also reviewed for additional studies.

study selection

To be included, studies had to be an observational study (e.g. cross-sectional, case–control, or cohort study) investigating the relationship between VAT and colorectal adenomas. For dose–response meta-analysis, studies had to provide the following information: a quantitative measure of VAT for at least three categories with the estimates of relative risks (odds ratio (OR), rate ratio, or hazard ratio), 95% confidence interval (CI), category-specific or total number of cases, and category-specific or total number of either noncases or person-years. Excluding a study that adjusted for intermediate variables such as IGF-1 [9], a total of 12 studies were included in our meta-analysis (supplementary Table S2, available at Annals of Oncology online). Of the 12 studies [7, 10–20], a total of 10 studies (6 cross-sectional studies, 4 case–control studies) [7, 10–18] were eligible for this dose–response meta-analysis. The procedure of study selection is summarized in Figure 1.

data extraction

From each study, the following information was extracted: the most fully adjusted OR and corresponding 95% CI in each category of VAT, category-specific range of VAT, category-specific or total number of cases, category-specific or total number of noncases, unit (cm², cm³) and assessment method (anatomical site, machine used) of VAT, adenoma subtype, first author’s name, publication year, study design, study population (country, sex, age at enrollment), and adjustment variables.

statistical analysis

In the investigation of objectively-assessed exposure and asymptomatic outcome, point estimates from cross-sectional and case–control studies become more comparable, because difference by study design in their susceptibility to each bias becomes less pronounced. For example as VAT was measured by a medical equipment rather than self-reported by participants, participants’ knowledge of their disease status at VAT assessment did not lead to recall bias in case–control studies. Likewise, as asymptomatic adenomas are detectable only at time of endoscopy, source population was defined as subjects who underwent an endoscopy across the study designs. Given the well-defined primary source population from which both cases and controls are easily sampled, selection bias was less likely in case–control studies. For these reasons, both cross-sectional and case–control studies were analyzed together in dose–response meta-analysis.

Furthermore, while measurement of VAT area (cm²) was relatively standardized, studies varied in abdominal region over which VAT volume (cm³) was quantified, which made VAT volume noncomparable across studies. Thus, dose–response meta-analysis was conducted only among studies that measured VAT area (6 studies [7, 10–14] of the 10 eligible studies [7, 10–18]). For linear dose–response meta-analysis assuming a linear relationship between visceral adiposity as measured by VAT area and adenoma risk, the method described by Greenland and Longnecker [21] was used to calculate study-specific ORs (linear slopes) and 95% CIs from the correlated ORs and 95% CIs extracted across categories of VAT area. In estimating study-specific linear trends, several approximations were made: the
midpoint of VAT area in each category was assigned to the corresponding OR; the width of the open-ended extreme categories was assumed to be the same as that of the adjacent interval; when the range of VAT area for each category was given separately for men and women, weighted average of the two midpoints using the number of each sex as the weight was assigned to the corresponding OR [12, 14]; when the distributions of cases and noncases were not provided, they were estimated if the analysis was based on quantiles and category-specific crude ORs and total number of cases and noncases were given [11, 12]. Then, the estimated study-specific ORs and variances were pooled using a random-effects model to calculate the summary OR and 95% CI. Forest plots of the linear dose–response meta-analysis were presented for ORs for each 25 cm² increment in VAT area (a unit area equivalent to the area of a square with sides of 5 cm).

To examine any potential nonlinear relationship between VAT area and adenoma risk, nonlinear dose–response meta-analysis was carried out based on the restricted cubic spline approach [22, 23]. For each study, cubic splines were modeled with three knots fixed at percentiles (10%, 50%, and 90%) of the whole distribution of VAT area, accounting for correlation across category-specific ORs and 95% CIs within each study [22]. This approach requires that studies have more than three categories of VAT area. The reference was set to 30 cm², the lowest value of the reported VAT area. Then, the derived curves were combined using multivariate random-effects meta-analysis [24]. The P value for nonlinearity was obtained from the test of the null hypothesis that the regression coefficient of the second spline transformation was equal to zero.

Heterogeneity in the relationship between VAT area and adenomas across studies was tested by Cochran’s Q test [25] and quantified by the percentage of total variation across studies that is attributable to true heterogeneity rather than to chance (I²) [26]. Subgroup analyses and meta-regression were conducted based on linear dose–response meta-analysis by a priori selected variables related to potential effect modifiers to identify sources of heterogeneity; by variables concerning methodological characteristics to assess study quality. Due to insufficient data, etiology heterogeneity by adenoma subtype was explored qualitatively. Potential for small study effects [27, 28], such as publication bias, was assessed visually using funnel plots and statistically using Egger’s test [29]. To check robustness of the results, diverse sensitivity analyses were carried out by running

Figure 1. Flowchart for study selection.
the influence analysis, repeating linear dose–response meta-analysis excluding the three studies [11, 12, 14] that made additional approximations, and conducting highest versus lowest meta-analysis that pooled ORs for the extreme categories of VAT area or volume using a random-effects model based on the 12 studies [7, 10–20]. To compare the relative importance of VAT and other adiposity indices (BMI, WC, SAT), additional highest versus lowest meta-analyses were carried out based on all 12 studies identified [7, 10–20]. To investigate whether VAT is associated with adenomas above and beyond the other adiposity indices, we compared the pooled OR unadjusted for BMI, WC, and SAT with the pooled OR adjusted for another adiposity index (BMI, WC, or SAT). This comparison was restricted to studies that provided both the unadjusted and adjusted ORs. Conversely, to investigate if adjustment for VAT attenuates associations between the other adiposity indices and adenomas, for each adiposity index we compared the pooled OR unadjusted for VAT with the pooled OR adjusted for VAT, restricting analyses to studies that presented both unadjusted and adjusted analyses. In addition, as a sensitivity analysis, we compared the pooled ORs for each of VAT, BMI, WC, and SAT that were not mutually adjusted for, which were obtained from studies that provided mutually unadjusted ORs for VAT and for at least one of the other adiposity indices.

For statistical significance, two-sided \( \alpha \) was set at 0.05. All statistical analyses were conducted using STATA 12 (StataCorp, College Station, TX).

results
dose–response meta-analysis

In the linear dose–response meta-analysis of six studies (three cross-sectional, three case–control studies) [7, 10–14], a total of

![Figure 2. Dose–response meta-analyses of VAT area and adenomas. (A) Linear dose–response meta-analysis; (B) nonlinear dose–response meta-analysis (reference = 30 cm²). Inner ticks on the x-axis represent data points contributed by the studies included in the meta-analysis.](image)
2776 cases were included with category-specific midpoints of VAT area ranging from 30 to 228 cm². The summary OR for each 25 cm² increase in VAT area was 1.13 (95% CI 1.05–1.21), with moderate heterogeneity ($I^2 = 62\%$, $P_{\text{heterogeneity}} = 0.02$) (Figure 2A). Small study effects, such as publication bias, were not indicated by the funnel plot (symmetrical shape, figure not shown) and Egger’s test ($P = 0.81$). In sensitivity analyses excluding one study at a time, the results did not change materially (data not shown). Even after excluding the study by Kang et al. [12] that showed the strongest association, the attenuated summary association was statistically significant with no evidence of heterogeneity (OR = 1.09, 95% CI 1.04–1.14, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.77$). When the analysis was conducted excluding the three studies [11, 12, 14] that made additional approximations, the results did not change materially except for a markedly reduced heterogeneity (OR = 1.12, 95% CI 1.04–1.21, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.80$). In the nonlinear dose–response meta-analysis, five studies [7, 10–12, 14] were included (2690 cases, range = 30–227 cm²), after excluding one study [13] that analyzed VAT area in three categories only. The dose–response curve suggested no evidence of nonlinearity ($P_{\text{non-linearity}} = 0.37$) (Figure 2B). Compared with 30 cm² of VAT area, the summary OR was 1.48 (95% CI 1.31–1.66) at 90 cm² and increased to 1.98 (95% CI 1.75–2.24) at 150 cm².

To explore robustness of a statistically significant direct association in the most inclusive dataset, highest versus lowest meta-analysis was carried out by additionally including studies that were not eligible for the dose–response meta-analysis (i.e. four studies that assessed VAT in volume; two studies that provided ORs for a binary VAT area). In the dataset including a total of the 12 studies [7, 10–20], higher VAT was associated with a statistically significantly increased odds of adenomas compared with lower VAT (OR = 1.76, 95% CI 1.41–2.19, $I^2 = 53\%$, $P_{\text{heterogeneity}} = 0.02$) (supplementary Figure S1, available at Annals of Oncology online).

**subgroup analysis**

In most of the subgroups defined by variables related to potential effect modifiers and methodological qualities, an increase in VAT area remained associated with statistically significant elevated odds of adenomas, suggesting robustness of the relationship (supplementary Table S3, available at Annals of Oncology online). In particular, the direct linear relationship was statistically significant regardless of adjustment for BMI and SAT, which suggests that visceral adiposity is an independent risk factor for adenomas above and beyond other adiposity indices. None of the stratifying variables explained the observed moderate heterogeneity, but our study is low powered to detect between-subgroup heterogeneity due to the limited number of studies.

Pertaining to etiologic heterogeneity by adenoma subtype, some studies reported that the mean or median VAT area was statistically significantly greater among people with advanced adenomas (diameter ≥1 cm, villous component, or high-grade dysplasia) than those with nonadvanced adenomas, or that VAT was more strongly associated with advanced adenomas than with nonadvanced adenomas (supplementary Table S4, available at Annals of Oncology online). By respective characteristic of adenomas, greater VAT area appeared to be more consistently associated with large size and multiplicity than with (tubulo)villous component and high-grade dysplasia in all seven studies that reported on this.

**highest versus lowest meta-analysis: VAT in comparison with other adiposity indices**

A positive association between VAT and adenomas remained statistically significant even after adjustment for BMI, WC, or SAT (Figure 3A–C). Conversely, adjustment for VAT substantially attenuated associations of BMI, WC, and SAT with adenomas (Figure 4A–C). In a sensitivity analysis that compared summary ORs mutually unadjusted for each of adiposity indices, VAT was generally a stronger risk factor than the other adiposity indices, although the magnitudes were not directly comparable (supplementary Figure S2a–c, available at Annals of Oncology online).

**discussion**

In our dose–response meta-analyses of six observational studies, VAT area was linearly associated with the odds of adenomas, with each 25 cm² increase in VAT area elevating the odds approximately by 13%. While there was a moderate degree of heterogeneity, it was strongly driven by a single study [12] that showed the strongest association among the six studies included. The direct association was robust, as it remained statistically significant after excluding the study by Kang et al. [12]; in most of the subgroups defined by variables related to potential effect modifiers and methodological aspects; in the highest versus lowest meta-analysis conducted in the dataset including the six additional studies [15–20]. There was consistent evidence that VAT may be more strongly associated with advanced adenomas.

Our meta-analyses provide strong evidence supporting the predominant role of VAT in linking excess adiposity and adenomas. First, a statistically significant direct association between VAT and adenomas persisted even after adjustment for BMI, WC, and SAT, whereas that of adenomas with each of BMI and WC was abolished upon adjustment for VAT. Indeed, in a study that simultaneously included three indices (BMI, WC, and VAT) in the same regression model, only VAT was a statistically significant risk factor for adenomas [11]. Second, SAT was not associated with adenomas regardless of adjustment for the other adiposity indices. Third, among summary ORs comparing the extreme categories of each of VAT, BMI, WC, and SAT that were not mutually adjusted for, VAT was the strongest risk factor for adenomas. These findings suggest that the observed associations of BMI and WC with colorectal neoplasia may be due to the correlations of BMI and WC with VAT; the presence of an association between WC and colorectal neoplasia independent of BMI may be attributable to the better capability of WC to capture VAT than BMI. Indeed, a study showed that VAT was statistically significantly more strongly correlated with WC than with BMI (men: 0.55 versus 0.46, women: 0.76 versus 0.60) [30].

Our results are consistent with the specific contribution of VAT to colorectal neoplasia and this has important implications, especially for men and Asians. Compared with women, men
### A: OR by adjustment for BMI

<table>
<thead>
<tr>
<th>First author, year</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>(Adjusted for BMI)</td>
<td></td>
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<tr>
<td>Nagata, 2014</td>
<td>1.90 (1.16, 3.13)</td>
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<tr>
<td>Yamaji, 2014</td>
<td>2.42 (1.46, 4.03)</td>
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<tr>
<td>Nam, 2010</td>
<td>1.41 (1.00, 2.01)</td>
</tr>
<tr>
<td>Yamamoto, 2010</td>
<td>1.08 (0.42, 2.81)</td>
</tr>
<tr>
<td>Yamaji, 2009</td>
<td>0.99 (0.71, 1.40)</td>
</tr>
<tr>
<td>Subtotal (I²=60.8%, P=0.037)</td>
<td>1.48 (1.06, 2.07)</td>
</tr>
</tbody>
</table>

| (Not adjusted for BMI) |                 |
| Nagata, 2014          | 1.64 (1.13, 2.38) |
| Yamaji, 2014          | 3.46 (2.35, 5.09) |
| Nam, 2010             | 1.43 (1.06, 1.94) |
| Yamamoto, 2010        | 0.99 (0.45, 2.20) |
| Yamaji, 2009          | 1.46 (1.03, 2.06) |
| Subtotal (I²=76.2%, P=0.002) | 1.71 (1.18, 2.46) |

### B: OR by adjustment for WC

<table>
<thead>
<tr>
<th>First author, year</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>(Adjusted for WC)</td>
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<tr>
<td>Yamaji, 2014</td>
<td>2.42 (1.46, 4.03)</td>
</tr>
<tr>
<td>Nam, 2010</td>
<td>1.52 (1.04, 2.21)</td>
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<tr>
<td>Subtotal (I²=51.9%, P=0.149)</td>
<td>1.86 (1.18, 2.92)</td>
</tr>
</tbody>
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| (Not adjusted for WC) |                 |
| Yamaji, 2014          | 3.46 (2.35, 5.09) |
| Nam, 2010             | 1.43 (1.06, 1.94) |
| Subtotal (I²=92.0%, P<0.001) | 2.21 (0.93, 5.24) |

### C: OR by adjustment for SAT

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<tr>
<th>First author, year</th>
<th>OR (95% CI)</th>
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<tr>
<td>(Adjusted for SAT)</td>
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<tr>
<td>Nagata, 2014</td>
<td>1.90 (1.16, 3.13)</td>
</tr>
<tr>
<td>Kang, 2010</td>
<td>3.09 (2.19, 4.36)</td>
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<tr>
<td>Subtotal (I²=59.8%, P=0.115)</td>
<td>2.51 (1.56, 4.02)</td>
</tr>
</tbody>
</table>

| (Not adjusted for SAT) |                 |
| Nagata, 2014          | 1.64 (1.13, 2.38) |
| Kang, 2010            | 3.56 (2.63, 4.81) |
| Subtotal (I²=90.0%, P=0.002) | 2.44 (1.14, 5.20) |

**Figure 3.** Meta-analysis of highest versus lowest category of VAT and adenomas. (A) By adjustment for BMI; (B) by adjustment for WC; (C) by adjustment for SAT.
Figure 4. Meta-analysis of highest versus lowest category of other adiposity indices and adenomas by adjustment for VAT. (A) For BMI; (B) for WC; (C) for SAT.
have higher VAT [30, 31] and thus, have a wider range of VAT with more in the top range. Considering our finding of a linear relationship between VAT and adenomas and assuming the same association for men and women, the risk of adenomas associated with VAT would be higher among men than among women. For instance in a healthy Caucasian population with mean age of 43.3 years, the mean and range of VAT area was 77 (3–290) cm² for women and 137 (3–482) cm² for men [30]. Based on our finding of 13% increased odds per 25 cm² increase in VAT area, on average, men would have an ~34% increased odds of adenomas compared with women, which may contribute to higher rates of colorectal neoplasia observed among men [32]. Similarly, compared with Caucasians, Asians have higher VAT for a given BMI due to their lower muscle mass and tendency toward visceral obesity [33]. In light of a linear association found between VAT and adenomas, the relatively higher VAT in Asians may contribute to higher rates of colorectal neoplasia observed in Asians in the normal range of BMI [32] and more pronounced ORs comparing extreme categories of VAT in Asian countries relative to non-Asian countries (supplementary Figure S3, available at Annals of Oncology online).

There are several strengths in our dose–response meta-analyses. First, this is the first meta-analysis that summarized the relationship between VAT and adenomas, demonstrating VAT as a principal mediator of excess adiposity and adenomas above and beyond the overall amount and distribution of adipose tissue. Second, by performing dose–response meta-analyses, we identified a linear relationship with the odds increasing by 13% for each 25 cm² increase in VAT area. Third, confounding by lifestyle factors is less likely to have affected our summary estimates. As the investigation of VAT and adenomas requires the use of costly medical service such as CT scan and endoscopy, most of the studies included recruited participants from asymptomatic individuals who underwent such procedures for a routine health checkup. Considering that lifestyle factors including diet and physical activity are important determinants of VAT and adenomas, studies conducted among health-conscious people whose lifestyle factors are likely to be more homogeneous than those among the general population are less prone to confounding by lifestyle factors. Fourth, albeit reviewed qualitatively, the consistent observation of a stronger association of VAT with advanced adenomas, which are the likely precursors to most colorectal cancers, suggests that VAT may be implicated in both development and promotion of adenomas. Finally, publication bias may be less of a concern as studies with costly and complex assessment of the exposure and outcome may be unlikely to remain unreported given the investment made.

Our dose–response meta-analyses have several limitations as well. First, meta-analyses of observational studies are prone to the same weaknesses as the included observational studies. Second, while the use of objective measurement of VAT minimized exposure measurement error within each study, the inevitable approximations made to conduct dose–response meta-analyses, as described in the methods section, introduced measurement error. Third, there is uncertainty about the temporal relationship between visceral obesity and adenomas. In most of the studies included, measurement of VAT by CT was done on the same day as endoscopy. Furthermore, as adenomas are asymptomatic, adenomas detected at endoscopy would have been present for a variable time period. Thus, a summary OR from our meta-analyses indicates the relative odds of ‘having’ adenomas associated with a difference in VAT area (i.e. prevalence OR). However, as adenomas are not malignant by themselves, it is unlikely that the presence of undetected adenomas affects VAT, precluding the possibility of reverse causation.

In conclusion, VAT may be the underlying mediator of the observed associations of BMI and WC with adenomas, continuing to increase adenoma occurrence within the range of 30–227 cm² of VAT area. While high VAT is strongly associated with adenomas, in a clinical setting, routine measurement of VAT is not likely to be feasible due to high expenses of CT and MRI and concern about exposure to ionizing radiation. Given that the combination of BMI and WC explained a greater proportion of variability in VAT [30], at least, the joint use of BMI and WC should be promoted in a clinical practice to identify those at high risk for colorectal neoplasia and thus, to inform screening guidelines. A better surrogate of VAT may be visceral adiposity index [34], a sex-specific index based on WC, BMI, triglycerides, and high-density lipoprotein cholesterol, when additional information is available. Future studies examining the relationship of visceral adiposity index or other surrogates of visceral adiposity with colorectal neoplasia are warranted to guide clinical application of visceral adiposity index for the prevention and surveillance of colorectal neoplasia.

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**disclosure**
The authors have declared no conflicts of interest.

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