Impact of body mass index on the risk of colorectal adenoma

in a metabolically healthy population

Running title: Metabolically healthy obesity and colorectal adenoma

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Abbreviations:

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMI: body mass index
CI: confidence interval
CRA: colorectal adenoma
CRC: colorectal cancer
FBG: fasting blood glucose
GGT: gamma-glutamyltransferase
HOMA-IR: homeostasis model assessment of insulin resistance
HDL-C: high-density lipoprotein-cholesterol
hsCRP: high sensitivity-C reactive protein
LDL-C: low-density lipoprotein-cholesterol
MHNW: metabolically healthy, normal-weight
MHO: metabolically healthy, but obese
OR: odds ratio

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Abstract

Metabolically healthy obese (MHO) states exist which seem to be protected from cardiovascular risks. Although obesity is a risk factor for colorectal adenoma (CRA), there has yet to be any study of the risks of CRA in MHO individuals. In this study, we compared CRA prevalence in MHO individuals versus metabolically healthy individuals who were normal in weight. This cross-sectional study involved 18,085 Korean adults (39.1 ± 6.7 years) who had a health checkup including a colonoscopy. High-risk CRA was defined as any adenoma over 1 cm, 3 or more adenomas, adenoma with a villous component, or high grade dysplasia. Multinomial logistic regression models were used to measure the associations between body mass index (BMI) and the risk of low-risk and high-risk CRA. Low-risk and high-risk CRA were present in 9.3 % and 1.4 % of the study population, respectively. After adjusting for age, sex, smoking, drinking, exercise, family history of colorectal cancer, education and use of analgesic and aspirin, compared with normal healthy individuals, the prevalence of low-risk and high-risk CRA was increased in MHO individuals [odds ratio, 1.44; 95% confidence interval (CI), 1.23-1.69 and 1.62; 95% CI, 1.09-2.41, respectively]. In fully adjusted models, the prevalence of low-risk and high-risk CRA was associated with increasing categories of BMI in a dose-response manner (P for trend <0.001 and 0.01, respectively). Thus, excess body weight, even in the absence of a metabolic unhealthy state, was found to be positively associated with increased presence of colorectal adenomas.

Keywords: Metabolically Healthy Obesity; Body Mass Index; Colorectal Adenoma
Introduction

Excess body weight, expressed as body mass index (BMI), is an important risk factor for colorectal cancer (CRC) and adenoma (CRA) in a sex-specific manner (1, 2), with higher BMIs associated with higher risks. Although the mechanisms underlying these associations are not fully understood, insulin resistance and related metabolic disturbances are considered the most plausible explanations (3). However, the prevalence of obesity-related metabolic disturbances varies widely among obese individuals (4, 5). For example, increased BMI is commonly, but not always, accompanied by insulin resistance and related disturbances. Based on previous findings, it is not clear whether obesity per se or the presence of co-existing metabolic risk factors (6) such as diabetes, metabolic syndrome, and insulin resistance is associated with CRC and CRA.

Recently metabolically healthy, as well as, metabolically unhealthy states have been recognized to exist among obese individuals (5, 7). A unique subset of these individuals, termed metabolically healthy obese (MHO) individuals, despite having excessive body fat, appear to have a favorable metabolic profile without obesity-related metabolic abnormalities including insulin resistance, proatherogenic lipoprotein profile, proinflammatory state, or hypertension (5, 7). Furthermore, previous studies showed that MHO individuals were not at an increased risk for cardiovascular diseases compared to normal-weight subjects (5, 8). Likewise, these individuals might not be at an increased risk for CRA or CRC, but no study has tested this hypothesis. This study evaluated the associations between BMI and CRA, established precursor lesions for CRC (9), through screening colonoscopies performed on individuals who are metabolically healthy determined by a range of anthropometric and biochemical measures.
Materials and Methods

Study population

The study population consisted of examinees who underwent a colonoscopy as part of a comprehensive health screening program at Kangbuk Samsung Hospital, Seoul, Korea from 2010 to 2011 (N=62,171). The purpose of the screening program is to promote health through early detection of chronic diseases and their risk factors. Such programs are popular in Korea (10). Additionally, in Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. About 60% of the participants were employees of various companies and local governmental organizations and their spouses with the remaining participants registering individually for the program.

For this analysis, we excluded participants with missing anthropometric measures and incomplete colonoscopies (Figure 1). Metabolically healthy participants were defined as those not having any metabolic abnormalities as follows (7, 11): 1) fasting blood glucose (FBG) ≥100 mg/dl or current use of blood glucose-lowering agents (12); 2) blood pressure ≥130/85 mmHg or current use of blood pressure-lowering agents (12); 3) elevated triglyceride levels ≥150 mg/dl or current use of lipid lowering agents (12); 4) low high-density lipoprotein-cholesterol (HDL-C) (HDL-C <40 mg/dl in men or <50 mg/dl in women) (12); and 5) insulin resistance as homeostasis model assessment of insulin resistance (HOMA-IR) ≥2.5 (13). We further excluded subjects with history of inflammatory bowel disease and factors that could affect the association between BMI and CRA. As some individuals met more than one criterion for exclusion, the total number of eligible subjects for the study was 18,085 (Figure 1).

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent as we only accessed data
retrospectively that were de-identified.

Measurements

Data on medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire while the physical measurements and serum biochemical parameters were measured by trained staff, all collected during the health examinations. Details regarding alcohol use included the frequency of intake per week and the average amount of intake per episode. Current smokers were identified and the weekly frequency of moderate- or vigorous-intensity physical activity assessed. Family history of CRC was defined as CRC in one or more first-degree relatives at any age. Self-reported use of aspirin and analgesics of any type over the past month were assessed. Body weight was measured in light clothing and no shoes to the nearest 0.1 kilogram using a digital scale. Height was measured to the nearest 0.1 centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Trained nurses measured sitting blood pressure with standard mercury sphygmomanometers.

Blood samples were taken from the antecubital vein after at least a 10-hour fast. Serum levels of uric acid, total cholesterol, and triglyceride were determined using an enzymatic colorimetric assay; low-density lipoprotein cholesterol (LDL-C) and HDL-C levels were determined using an homogeneous enzymatic colorimetric assay; and alanine aminotransferase (ALT) and aspartate aminotransferase levels were determined by photometry using a Modular Analytics D2400 (Roche Diagnostics, Tokyo, Japan). Serum hsCRP level was determined using a particle-enhanced immunoturbidimetric assay on the Modular Analytics P800 apparatus (Roche Diagnostics). Serum insulin level was measured using electrochemiluminescence immunoassay on the Modular Analytics E170 apparatus (Roche Diagnostics) and serum fasting glucose level was measured using the hexokinase
method on the Cobas Integra 800 apparatus (Roche Diagnostics; Rotkreuz, Switzerland).

Insulin resistance was assessed with HOMA-IR according to the following equation: fasting blood insulin (uU/ml) × FBG (mmol/l) / 22.5. The Laboratory Medicine Department at Kangbuk Samsung Hospital in Seoul, Korea has been accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL). The laboratory participates in the CAP (Collage of American Pathologists) Survey Proficiency Testing.

Colonoscopy and histologic examination

Following careful bowel preparation with 4 liters of polyethylene glycol–electrolyte oral lavage solution (Taejoon Pharm, Seoul, Korea), colonoscopy was performed on each subject by one of 13 experienced gastroenterologists using the EVIS LUCERA CV-260 colonoscope (Olympus, Tokyo, Japan) from the rectum to the cecum. All polypoid lesions were biopsied or removed and histologically assessed by experienced pathologists. Polyps were classified by number, size, and histologic characteristics (tubular, tubulovillous or villous adenoma; hyperplastic polyp; sessile serrated polyp [also known as sessile serrated adenoma] or traditional serrated adenoma). Hyperplastic polyps or other findings including diverticuli, hemorrhoids, anal fissure, and angiodysplasias were classified as normal colonoscopic findings in this study. The grade of dysplasia was classified as low or high grade. High-risk adenoma was defined as any adenoma larger than 1 cm, three or more adenomas, any adenoma with a villous component, or high grade dysplasia (14). Subjects simultaneously diagnosed with high-risk and low-risk adenomas were classified as high-risk adenoma.

In a sensitivity analysis (supplementary tables 1 and 2), study subjects were categorized into one of four groups: 1) control group whose colonoscopy detected neither hyperplastic polyps nor adenomatous polyps; 2) hyperplastic polyps only; 3) low-risk adenoma; and 4) high-risk
adenoma. Subjects simultaneously diagnosed with hyperplastic polyps and adenomatous polyps were classified as either low-risk or high-risk adenoma according to their findings. For example, subjects with hyperplastic polyps and low-risk adenoma were classified as low-risk adenoma, whereas subjects with hyperplastic polyps and low-risk and high-risk adenomas were classified as high-risk adenoma.

**Statistical analyses**

Descriptive statistics were used to summarize the characteristics of participants by BMI categories in men and women. The BMI classification developed for Asian population was used (15): metabolically healthy underweight (MHU) = BMI <18.5 kg/m²; metabolically healthy normal-weight (MHNW) = BMI of 18.5 to 23 kg/m²; metabolically healthy overweight (MHOW) = BMI of 23 to 25 kg/m²; and metabolically healthy obese (MHO) = BMI ≥25 kg/m². The distribution of continuous variables was evaluated and appropriate transformations were performed during analysis, as needed. Odds ratios (ORs) were used to measure the association of BMI categories with the prevalence of one or more low-risk adenomas and one or more high-risk adenomas. In the main analyses, controls are subjects without any adenoma. Then in sensitivity analysis (supplementary tables 1 and 2), the controls are subjects without any adenoma or hyperplastic polyp. Multinomial logistic regression models were used to estimate ORs and 95 percent confidence intervals (95% CIs) after adjusting for potential confounders. The models were initially adjusted for age and sex, then for smoking, alcohol intake, exercise, educational level, and family history of CRC. To determine linear trends of prevalence, the number of categories or quartiles was used as a continuous variable and tested on each model. Subgroup analyses were conducted according to gender, age group (<50 vs ≥ 50 years of age), and lifestyle (current smoker vs noncurrent smoker. <20 vs ≥ 20 g of alcohol per day, <1
time/week vs ≥1 time/week of regular exercise); and interactions by subgroups were tested using the likelihood ratio tests (lrtest in STATA) comparing models with and without multiplicative interaction terms.

To compare the impact of BMI on CRA in the metabolically healthy population versus overall population, analyses were performed not restricted to metabolically normal subjects (supplementary tables 3 and 4).

The statistical analysis was performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA). All reported P values are two tailed, and comparisons where p <0.05 were considered statistically significant.

Results

With 7,179 women (39.7%) and 10,906 men (60.3%), the mean age and BMI of the 18,085 participants were 39.7 years (SD, 6.8) and 22.6 kg/m² (SD, 2.7, range 14.4-35.7), respectively. The baseline characteristics of the study participants in relation to BMI categories are outlined in Tables 1 and 2. Only for women was age positively associated with the BMI categories. For both men and women, current alcohol use, exercise, systolic and diastolic blood pressure, FBG, total cholesterol, triglycerides, uric acid, ALT, hsCRP, and HOMA-IR were positively associated with the BMI categories, whereas HDL-C was inversely associated with the BMI categories. The proportion of current smokers was the highest in MHU for men and in MHU and MHNW for women.

Table 3 shows the results of the multinomial logistic analyses with OR corresponding to 95% CIs of BMI categories for the prevalence of low-risk and high-risk adenoma. Of the 18,085 subjects, 1,674 subjects (9.3%) had low-risk adenomas and 248 subjects (1.4%) had high-risk adenomas. We first analyzed the relationships between the baseline BMI categories and each outcome adjusting for age and sex. Then, we adjusted for age, sex, smoking, drinking, regular exercise, and interactions by subgroups.
exercise, family history of colon cancer, education level, aspirin use, and analgesic use. In the
multivariate models, the prevalence of low-risk and high-risk CRA was associated with
increasing categories of BMI categories in a dose-response manner (P for trend <0.001 and
0.01, respectively). Compared to the MHNW group, the MHO group was at a significantly
increased prevalence of both low-risk adenomas (OR, 1.44; 95% CI, 1.21-1.71) and high-risk
adenomas (OR 1.59; 95% CI, 1.04-2.43). In order to explore whether the association between
BMI categories and CRA was mediated by HOMA-IR or hsCRP levels, we performed
additional analysis by adjusting for HOMA-IR and hsCRP levels. The results did not change.
Further adjusting for glucose, SBP, and DBP did not materially alter the estimates (data not
shown).

The associations between the BMI categories and the prevalence of low-risk and high-risk
adenomas were also examined by gender (Table 4). For men, an increase across BMI
categories was positively associated with the prevalence of high-risk adenomas, as well as,
low-risk adenomas in a dose-response manner (P for trend <0.001 and 0.02, respectively).
For women, the BMI categories were not statistically significantly related to low-risk
adenomas, and the associations between the BMI categories and the prevalence of high-risk
adenomas seemed to be nonlinear. The MHOW was positively associated with increased
prevalence of high-risk adenomas (OR, 2.64; 95% CI, 1.30-5.36) whereas MHO was not
statistically positively associated with high-risk adenoma. The overall interaction between
gender and BMI categories for both low-risk adenoma and high-risk adenoma were not
significant (p for interaction =0.48).

The associations between the BMI categories and the prevalence of low-risk and high-risk
adenomas were similar across the subgroups of the study participants with no significant
interactions according to age group (<50 vs ≥ 50 years of age), and lifestyle (current smoker
vs noncurrent smoker. <20 vs ≥ 20 g of alcohol per day, <1 time/week vs ≥1 time/week of
In a sensitivity analysis, we examined the association of BMI categories with the prevalence of low-risk and high-risk adenomas with the control group consisting of subjects without hyperplastic polyps nor adenomas. These analyses did not change any of the adenoma associations qualitatively (supplementary tables 1 and 2).

Supplementary tables 3 and 4 show the impact of BMI on CRA in the population not restricted to the metabolically healthy population. Overall, the associations between obesity and CRA were similar to that in the metabolically healthy population.

**Discussion**

The present study demonstrates that MHO individuals had a higher prevalence of high-risk CRA, as well as, low-risk CRA compared to MHNW individuals.

Previous studies have suggested that a higher BMI is associated with an increased risk of low-risk and high-risk CRA (16, 17). An important finding of our study is that this association exists even in metabolically healthy subjects selected exclusively for not having any metabolic syndrome components and insulin resistance. This suggests that increased BMI, even in the absence of a metabolic unhealthy state, can be an important risk factor for both low-risk and high-risk CRA. Another study showed that increased BMI and total body fat percentage, as a promoting factor, appears to increase adenoma growth (18). Our study supports that excess fat per se, even without metabolic abnormalities, is an independent risk factor for the development of CRA and its progression.

To our knowledge, this is the first study to address the hypothesis that MHO phenotype is a risk factor for pre-cancerous lesions. Our findings raise the possibility that MHO individuals, a subset of obese individuals, might be protected from the cardiovascular risk standpoint but not protected from the cancer risk standpoint. Further studies are needed to address MHO...
phenotype as a possible risk for other cancers where obesity is a known risk factor such as kidney, prostate, pancreas, breast, and endometrial cancers (19, 20).

With regard to the relationship between BMI, CRA and CRC by sex, existing evidence suggests that the associations between obesity, CRA and CRC are more consistent and stronger among men than women (1, 2, 21-23). Our study finding showed that higher BMI categories were significantly associated with increased prevalence of both low-risk and high-risk CRA in men but were inconsistent in women, showing a significantly increased prevalence of high-risk CRA only in women with MHO: however, given the wide confidence limits for high-risk adenomas in women, it is difficult to exclude the effects of chance and characterize the occurrence pattern in any way. Previous studies reported weight change in addition to BMI was also independent factor for CRA or CRC (24, 25), especially in women (24). Also for women, the female hormonal status can affect the association between BMI and CRA (26). In this study, data on weight change, oral contraceptive use, or hormone therapy were not available for analysis. Additionally, the inconclusive result for women can be explained by the small number of obese women, which may be insufficient to establish a relationship and lead to imprecise estimates.

In this study, the prevalence of MHO phenotype was 23.9 % in obese individuals, lower than that in previous studies, with estimate as high as 30% in obese individuals (4, 5). Similarly, compared with previous reports (30), the prevalence of CRA was lower in this study, which is not unexpected due to our stringent criteria for MHO. One challenge in evaluating CRA risk in the MHO phenotypes is the lack of a uniform definition for MHO. In this study, we defined metabolically healthy phenotype as subjects without any metabolic syndrome components and insulin resistance, which are commonly used to define MHO individuals (7).

The mechanisms that link increased BMI and CRA are not fully understood, though several
possibilities have been raised (3, 31, 32). Insulin resistance is considered a key mechanism underpinning the obesity-colon cancer link (3, 31). In this metabolically healthy population, the positive association between increased BMI and CRA remained significant even after adjusting for metabolic parameters including HOMA-IR. CRA might be not necessarily related to insulin resistance in obese individuals (33). Another potential mechanism for colon carcinogenesis can be obesity-related inflammation. In our study, a significant association between increased BMI and CRA remained even after adjusting for CRP levels. A recent cross-sectional study reported a significant positive relationship between circulating levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) and CRA, but a weaker, non-significant association between CRP and CRA (34). TNF-α and IL-6, inflammatory cytokines secreted by adipose tissue, were found to be involved in the early development of colorectal neoplasia (34, 35). In our study, IL-6 and TNF-α levels were not available, so we could not exclude obesity-related inflammation as a possible mediator between obesity and CRA.

An association between excess fat per se and CRA in MHO phenotypes can be explained by altered adipocytokines. Adipose tissue is an important endocrine organ secreting numerous adipokines consisting of hormones, cytokines, and other signaling molecules that play roles in energy balance, inflammation, insulin sensitivity, and angiogenesis (36-38). Altered adipokine secretion from the adipose tissue, such as leptin and adiponectin, is considered a potential mediator for obesity-related colon cancer (39-42). Colon epithelial cells express adiponectin and leptin receptors, supporting the potential of adiponectin and leptin to influence regulation of cellular processes within the colon (43). A recent study showed that adiponectin directly inhibits colon cancer cell proliferation (44). Leptin regulates proliferation in CRC by activating mitogenic and anti-apoptotic signaling pathways (45, 46). Moreover, there is evidence for interactive effects of adiponectin and leptin in the early stage of colorectal tumorigenesis, distinct from their involvement in insulin resistance (47).
Therefore, studies that further assess markers specifically indicating increased adipose tissue will be helpful for establishing MHO as a risk factor for CRA or CRC.

There are several limitations to this study. First, the definition of insulin resistance used in this study is based on HOMA-IR and not on euglycemic insulin clamp, a reference method for assessing insulin resistance (48), which is invasive and not feasible in large populations. A second limitation is the use of BMI as a measure of obesity as it cannot distinguish between fat tissue and lean tissue. If the MHO group in this study has higher lean tissue than fat mass, the association between higher BMI categories and CRA could be attenuated. Third, we were unable to include dietary information, which could be a possible confounder for CRA (49). Another limitation is that a cross-sectional design precludes the determination of causality; however, the strength of our study design is that individuals having a first-time screening colonoscopy were included, minimizing the possibility of reverse causation. Lastly, our findings cannot be simply extrapolated to other populations.

In conclusion, excess body weight, even in the absence of a metabolic unhealthy state, was associated with increased presence of both low-risk and high-risk CRA, established precursor lesions for CRC, possibly suggesting that the mechanisms linking excess body weight and CRA risk may go beyond insulin resistance. Further studies are needed to address MHO as a possible risk factor for obesity-related cancers.

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References


24. Nock NL, Thompson CL, Tucker TC, Berger NA, Li L. Associations between obesity and changes in adult BMI over time and colon cancer risk. Obesity (Silver Spring) 2008;16:1099-104.


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<th>Characteristics</th>
<th>Overall</th>
<th>MHU (&lt;18.5)</th>
<th>MHNW (18.5-22.9)</th>
<th>MHOW (23.0-24.9)</th>
<th>MHO (≥25.0)</th>
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<td>68.0 (55.0-86.0)</td>
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<td>86.0 (67.0-108.0)</td>
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<td>23.0 (18.0-32.0)</td>
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<td>HOMA-IR‡</td>
<td>0.63 (0.43-0.93)</td>
<td>0.34 (0.21-0.50)</td>
<td>0.52 (0.35-0.73)</td>
<td>0.68 (0.47-0.96)</td>
<td>0.87 (0.59-1.19)</td>
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Data are * means (standard deviation), † medians (interquartile range), or percentages. Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; MHU, metabolically healthy underweight; MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese. ‡ ≥ 20 g of ethanol per day; § ≥ 1 time per week
Table 2. Baseline characteristics of metabolically healthy participants who by BMI category among 7,179 women at health checkup center of Kangbuk Samsung Hospital in 2010-2011

<table>
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<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>MHU (&lt;18.5)</th>
<th>MHNW (18.5-22.9)</th>
<th>MHOW (23.0-24.9)</th>
<th>MHO (≥25.0)</th>
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<td>Current smoke (%)r</td>
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<td>2.9</td>
<td>2.9</td>
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<td>Alcohol intake (%)‡</td>
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<td>39.5</td>
<td>49.0</td>
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<td>Analgesics use (%)</td>
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<td>5.6</td>
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<td>66.5 (6.4)</td>
<td>68.2 (6.7)</td>
</tr>
<tr>
<td>Glucose (mg/dl)*</td>
<td>86.8 (7.3)</td>
<td>84.6 (8.3)</td>
<td>86.7 (7.3)</td>
<td>87.9 (6.5)</td>
<td>88.8 (5.9)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)*</td>
<td>189.8 (31.3)</td>
<td>182.0 (29.2)</td>
<td>188.4 (30.7)</td>
<td>194.8 (31.8)</td>
<td>202.3 (32.7)</td>
</tr>
<tr>
<td>HDL-C mg/dl*</td>
<td>67.9 (12.3)</td>
<td>71.8 (13.4)</td>
<td>68.5 (12.3)</td>
<td>65.4 (11.5)</td>
<td>62.8 (10.3)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)†</td>
<td>62.0 (51.0-79.0)</td>
<td>59.0 (49.0-70.0)</td>
<td>61.0 (50.0-76.0)</td>
<td>68.0 (55.0-87.0)</td>
<td>75.0 (60.0-96.0)</td>
</tr>
<tr>
<td>ALT (U/l)†</td>
<td>15.0 (12.0-20.0)</td>
<td>15.0 (12.0-19.0)</td>
<td>15.0 (12.0-20.0)</td>
<td>16.0 (13.0-21.0)</td>
<td>19.0 (14.0-24.0)</td>
</tr>
<tr>
<td>hsCRP (mg/l)†</td>
<td>0.30 (0.30-0.60)</td>
<td>0.30 (0.20-0.30)</td>
<td>0.30 (0.20-0.50)</td>
<td>0.40 (0.30-0.70)</td>
<td>0.60 (0.30-1.30)</td>
</tr>
<tr>
<td>HOMA-IR†</td>
<td>0.65 (0.43-0.95)</td>
<td>0.49 (0.31-0.72)</td>
<td>0.62 (0.40-0.88)</td>
<td>0.80 (0.54-1.10)</td>
<td>0.94 (0.68-1.31)</td>
</tr>
</tbody>
</table>

Data are *means (standard deviation), †medians (interquartile range), or percentages.
Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; MHU, metabolically healthy underweight; MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese.
‡ ≥ 20 g of ethanol per day ; § ≥ 1 time per week
Table 3. Associations between body mass index and colorectal adenoma in 18,085 metabolically healthy participants among health checkup examinees at Kangbuk Samsung Hospital in 2010-2011

<table>
<thead>
<tr>
<th>BMI (kg/m²) category</th>
<th>Person</th>
<th>Prevalent case</th>
<th>Age-sex -adjusted OR (95% CI)</th>
<th>Multivariate OR⁺ (95% CI)</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low-risk adenoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHU (&lt;18.5)</td>
<td>915</td>
<td>57</td>
<td>0.96 (0.72-1.28)</td>
<td>0.90 (0.61-1.33)</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>MHNW (18.5-22.9)</td>
<td>9,337</td>
<td>754</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>MHOW (23.0-24.9)</td>
<td>4,501</td>
<td>470</td>
<td>1.11 (0.98-1.26)</td>
<td>1.17 (1.01-1.37)</td>
<td>1.17</td>
<td>1.17</td>
</tr>
<tr>
<td>MHO (≥25.0)</td>
<td>3,332</td>
<td>393</td>
<td>1.29 (1.12-1.47)</td>
<td>1.44 (1.23-1.69)</td>
<td>1.44</td>
<td>1.44</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>High-risk adenoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHU (&lt;18.5)</td>
<td>915</td>
<td>7</td>
<td>0.85 (0.39-1.85)</td>
<td>0.69 (0.24-1.96)</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>MHNW (18.5-22.9)</td>
<td>9,337</td>
<td>105</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>MHOW (23.0-24.9)</td>
<td>4,501</td>
<td>78</td>
<td>1.35 (0.99-1.83)</td>
<td>1.50 (1.04-2.16)</td>
<td>1.48</td>
<td>1.48</td>
</tr>
<tr>
<td>MHO (≥25.0)</td>
<td>3,332</td>
<td>58</td>
<td>1.44 (1.02-2.01)</td>
<td>1.62 (1.09-2.41)</td>
<td>1.59</td>
<td>1.59</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

⁺Model 1: adjusted for age and sex, smoking status, alcohol intake, regular exercise, family history of colon cancer, educational level, analgesic and aspirin use; model 2: model 1 plus adjusted for HOMA-IR and hsCRP

Abbreviations: BMI, body mass index; CI, confidence intervals; OR, odds ratios; MHU, metabolically healthy underweight; MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese.
Table 4. Associations between body mass index and colorectal adenoma by gender in 18,085 metabolically healthy participants among health checkup examinees at Kangbuk Samsung Hospital in 2010-2011

<table>
<thead>
<tr>
<th>BMI categories (kg/m²)</th>
<th>MHU (&lt;18.5)</th>
<th>MHNW (18.5-22.9)</th>
<th>MHOW (23.0-24.9)</th>
<th>MHO (≥25.0)</th>
<th>P value for trend</th>
</tr>
</thead>
</table>

**Men**

| Number=10,906 | 215 | 4,494 | 3,445 | 2,752 |
| Prevalent case of low-risk adenoma (%) | 9.3 | 9.8 | 11.4 | 12.3 |
| Prevalent case of high-risk adenoma (%) | 1.4 | 1.3 | 1.6 | 1.8 |
| aOR* (95% CI) for low-risk adenoma | 0.92 (0.52-1.60) | 1.00 (reference) | 1.21 (1.02-1.43) | 1.47 (1.24-1.75) | <0.001 |
| aOR* (95% CI) for high-risk adenoma | 0.85 (0.24-3.03) | 1.00 (reference) | 1.31 (0.86-1.98) | 1.66 (1.08-2.56) | 0.02 |

**Women**

| Number=7,179 | 700 | 4,843 | 1,056 | 580 |
| Prevalent case of low-risk adenoma (%) | 5.3 | 6.5 | 7.2 | 9.7 |
| Prevalent case of high-risk adenoma (%) | 0.6 | 1.0 | 2.1 | 1.6 |
| aOR* (95% CI) for low-risk adenoma | 0.87 (0.51-1.49) | 1.00 (reference) | 1.00 (0.67-1.49) | 1.34 (0.84-2.14) | 0.23 |
| aOR* (95% CI) for high-risk adenoma | 0.38 (0.05-2.85) | 1.00 (reference) | 2.64 (1.30-5.36) | 1.14 (0.33-3.94) | 0.06 |

Note: P = 0.48 for the overall interaction between gender and BMI categories for low-risk adenoma and high-risk adenoma (adjusted model)

*Adjusted for age and sex, smoking status, alcohol intake, regular exercise, family history of colon cancer, educational level, analgesic and aspirin use

Abbreviations: BMI, body mass index; CI, confidence intervals; OR, odds ratios; MHU, metabolically healthy underweight; MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese.
Figure legend

Figure 1. Flow diagram for the selection of study subjects
Participants who underwent a comprehensive health checkup at Kangbuk Samsung Hospital in Seoul, Korea from 2002 to 2009 (n=62,171)

**Exclusions (n= 6,853)**
- An incomplete colonoscopy or failure of an adequate biopsy (n=6,701)
- Missing data on anthropometry (n= 170)

Potential participants (n=55,318)

**Exclusions (n=32,041)**
- Pre-diabetes, diabetes or a current use of blood glucose-lowering agents (n= 13,177)
- Pre-hypertension, hypertension or a current use of blood pressure-lowering agents (n= 17,633)
- Hypertriglyceridemia, low HDL cholesterol or a current use of lipid lowering agents (n= 17,246)
- Insulin resistance defined as HOMA-IR >2.5 (n= 2,619)

Metabolically healthy participants (n=23,277)

**Exclusions (n= 5,192)**
- A history of prior colorectal surgery, polypectomy, or colonic examinations (n= 4,736)
- A history of malignancy (n= 549)
- A history of inflammatory bowel disease (n= 104)
- Detected as having colorectal carcinoid tumor during this study (n= 28)
- Detected as having colorectal adenocarcinoma during this study (n= 7)

**Metabolically healthy participants included for the analysis (n= 18,085)**
Impact of body mass index on the risk of colorectal adenoma in a metabolically healthy population

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