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BMI and Weight Changes and Risk of Obesity-related Cancers: A Pooled European Cohort Study

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Abstract

Background: Obesity is an established risk factor for several cancers. Adult weight gain has been associated with increased cancer risk, but studies on timing and duration of adult weight gain are relatively scarce. We examined the impact of BMI (body mass index) and weight changes over time, as well as timing and duration of excess weight, on obesity- and non-obesity-related cancers.

Methods: We pooled health data from six European cohorts, and included 221,274 individuals with two or more height and weight measurements during 1972-2014. Several BMI and weight measures were constructed. Cancer cases were identified through linkage with national cancer registries. Hazard ratios (HRs) of cancer with 95% confidence intervals (CIs) were derived from time-dependent Cox regression models.

Results: During follow-up, 27,881 cancer cases were diagnosed; 9,761 were obesity-related. The HR of all obesity-related cancers increased with increasing BMI at first and last measurement, maximum BMI, and longer duration of overweight (males only) and obesity. Participants being overweight before age 40 had an HR of obesity-related cancers of 1.16 (95%CI 1.02, 1.32) and 1.15 (95%CI 1.04, 1.27) in males and females, respectively, comparing those not overweight. The risk increase was particularly high for endometrial (70%), male renal cell (58%), and male colon cancer (29%). No positive associations were seen for cancers not regarded as obesity-related.

Conclusions: Adult weight gain was associated with increased risk of several major cancers. The degree, timing and duration of overweight and obesity also seemed to be important. Preventing weight gain may reduce the cancer risk.

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Key words

Obesity-related cancers, BMI and weight changes, cohort study

Key Messages

- Duration of overweight (males only) and obesity over time were associated with increased risk of all obesity-related cancers combined.
- Being overweight before age 40 increased the risk of all obesity-related cancers by approximately 15%, with higher risks in particular for endometrial (70%), male renal cell (58%), and male colon (29%) cancer.
- Preventing weight gain may be an important public health strategy to reduce the cancer risk.

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Introduction

Obesity is a major global health challenge. Worldwide, the overall prevalence of obesity (body mass index (BMI) ≥30 kg/m^2) among adult was 12% in 2015, and 5.4% of BMI-related deaths were due to cancer among obese persons.[1] In 2016, an IARC (International Agency for Research on Cancer) evaluation confirmed that excess body fatness was causally related to cancers of the oesophagus (adenocarcinoma), colon and rectum, kidney (renal cell carcinoma), endometrium and breast in postmenopausal women.[2] In addition, the IARC evaluation identified eight more cancers as causally related to excess body fat.[2] A 2017 umbrella review of almost 200 meta-analyses largely confirmed these findings.[3]

In a 2015 meta-analysis of prospective observational studies, each 5 kg increase in adult weight gain was associated with increased risk of postmenopausal breast (11%), endometrial (39%) and ovarian cancer (13%), and male colon cancer (9%).[4] A longitudinal study of postmenopausal women in the US showed that longer duration of overweight and obesity during adulthood increased the incidence of obesity-related cancers combined, postmenopausal breast cancer, and colon, endometrial and kidney cancer.[5] Also, a follow-up study from 2017 demonstrated a dose-response association of weight gain with several cancers.[6]

The 2018 report on Body fatness and weight gain and the risk of cancer from the World Cancer Research Fund concluded, however, that there was strong evidence of an association between weight gain in adulthood and increased risk of postmenopausal breast cancer only. Consequently, more research is needed on the association between weight gain and other obesity-related cancers.[7] Also studies on timing and duration of adult weight gain are relatively scarce.[8-10]

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Within the Metabolic Syndrome and Cancer Project (Me-Can 2.0), a pooled analysis of six European cohorts, we examined the impact of BMI and weight changes over time, duration of overweight and obesity, and age at first overweight measurement on incidence of obesity-related cancers. For comparison, we also displayed results for non-obesity-related cancers.

Material and Methods

The Me-Can 2.0 Project

The Me-Can 2.0 project is an expansion of the previous Me-Can 1.0 project,[11] and pools data from six cohorts in Austria (Vorarlberg Health Monitoring and Prevention Programme), Norway (Norwegian Counties Study, Age 40 Programme, and Oslo Study I), and Sweden (Västerbotten Intervention Programme and Malmö Preventive Project). All individuals in the cohorts have undergone one or more health examination(s), including measurements of height, weight, and circulating levels of glucose and triglycerides. We had no information available on ethnicity or place of birth.

In this study, we only included adults with two or more height (≥ 100 cm) and weight (≥ 35 kg) measurements during 1972-2014, obtained at least three years apart, and before the first cancer diagnosis (n=221,274) (Figure 1).

Exposure

Height and weight were measured at each health examination.[11] BMI was calculated as weight (kg) divided by the squared value of height (m), and categorized according to the World Health Organization (WHO);[12] BMI (kg/m^2) <18.5 (underweight), 18.5-24.9 (normal

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weight), 25.0-29.9 (overweight), ≥30.0 (obese). We used the second measurement as baseline for follow-up.

Several BMI and weight measures were constructed:

1. BMI at first and last measurement.
2. Maximum BMI measured.
3. BMI change since first measurement.
4. Weight change since first measurement.
5. Cumulated overweight-years (OWYs) calculated as the number of years being overweight (BMI 25.0-29.9 kg/m^2) since first measurement, assuming a linear change in BMI between measurements. All BMI measurements and all years between first and last measurement were included.
6. Cumulated obesity-years (OBYs) calculated in a similar way as in point 5 for BMI ≥30.0 kg/m^2.
7. Based on the first two measurements, five BMI-trajectories were made (including 92% of the study population).
8. Age at first measurement with BMI ≥25 kg/m^2 (<40, 40-49 years).

Outcome

After the second health examination, the individuals were followed until their first cancer, emigration, death, or end of follow-up (Austria and Sweden; 2014, Norway; 2012), whichever occurred first. Incident cancers were identified through linkages with national cancer registries.[13-15] In Norway and Sweden, the cohorts were also linked to population registries for vital status. Cancers were coded according to ICD-7/10, ICD-O-2/3 and

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SNOMED for topography and morphology. We studied all obesity-related cancers combined (cancers of the oesophagus (adenocarcinoma), gastric cardia, colon, rectum, liver, gallbladder, pancreas, breast (postmenopausal), endometrium, ovary, kidney (renal cell), and thyroid gland, and meningioma and multiple myeloma) and specific obesity-related cancers, such as breast (postmenopausal), endometrial, colon, and renal cell cancer.[2] Results for rectal, pancreatic, ovarian and other obesity-related cancers as well as non-obesity-related cancers are presented in the Supplementary Material.

Potential Confounders

The following factors were considered potential confounders and were adjusted for in the analyses: Smoking status (never, former, current smokers (divided into pack-years, <5, 5-13.4, ≥13.5 pack-years or missing)), parity (0, 1, 2, 3, ≥4), age at first birth (<20, 20-24, 25-29, 30-34, ≥35), physical activity (sedentary, light, moderate), education (Norway; compulsory, intermediate, tertiary, and Sweden; elementary school, junior secondary school, upper secondary school and university education), and triglycerides-glucose index (TyG index; a measure of insulin resistance)[16;17] (<7, 7-7.9, 8-8.4, 8.5-8.9, ≥9). Information on smoking status was available in all cohorts, whereas information on reproductive history (Norwegian cohorts), physical activity and education (Norwegian and Swedish cohorts), and TyG index (mostly Austrian and Swedish cohorts) was only available in some. Smoking status was included in all models, whereas the other potential confounders were included in cancer-specific models.

Statistical Analysis

Cox regression models with age as the time metric were fitted to obtain hazard ratios (HRs) with 95% confidence intervals (95% CIs). Tests for linear trend over BMI-categories were

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conducted using the BMI-variables as continuous variables. Statistical tests were two-sided. Some of the included variables were time-dependent; smoking status, BMI at last measurement, maximum BMI, BMI change, weight change, OWY, OBY and age at first measurement with BMI ≥ 25 changed at each measurement. The BMI and weight metrics were first included one at a time in separate models, except for OWY and OBY being included simultaneously. Thereafter, some of the metrics (BMI at last measurement, maximum BMI, BMI change, weight change, OWY and OBY) were included in models with adjustment for BMI at first measurement.

All models were adjusted for age at first measurement and at baseline, country, and smoking status. Cancer-specific adjustments were made in sensitivity analyses within the cohorts. Postmenopausal breast, endometrial, and ovarian cancer were additionally adjusted for parity, age at first birth, physical activity and education. Colon and pancreatic cancer were additionally adjusted for TyG index, physical activity and education. To explore the possibility of reverse causation, follow-up started one year after the health examinations in separate analyses.

The data was analyzed using IBM SPSS Statistics 23 and Stata/IC 14.0.[18;19]

Ethical and Legal Considerations

The Me-Can 2.0 project was approved by ethical committees in the respective countries.

Results

The study cohort consisted of 107,422 males and 113,852 females (Table 1). Altogether 32.4% of the participants had three health examinations, 17.2% participated in four or more. Mean number of examinations was 2.7 (range; 2-6). Average time between first and

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last health examination was 10.3 years (range; 3.0-23.6 years). Mean age at second health examination was 48.0 years (range; 19.0-85.0 years), and mean BMI was 25.6 kg/m^2 (males 26.0 kg/m^2; females 25.2 kg/m^2). The majority of the participants (53.8%) were never-smokers.

The individuals were followed for an average of 17.6 years (range; 0.0 – 36.6 years), constituting 3.9 million person-years. During follow-up, 27,881 cancers were diagnosed; 9,761 (35.0%) were obesity-related (Table 2).

The HR of all obesity-related cancers increased with increasing BMI at first and last measurement and maximum BMI (Table 3). One unit increase in BMI (HR 1.02, 95%CI 1.01, 1.03) and 5 kg increase in weight (HR 1.05, 95%CI 1.02, 1.07) were associated with increased risk in females. Duration of overweight (males) and obesity over time were also associated with risk; the HRs for OWY and OBY were 1.01 (95%CI 1.01, 1.02) and 1.04 (95%CI 1.03, 1.05) in males, and the HR for OBY was 1.04 (95%CI 1.03, 1.05) in females. Males being obese at the first two measurements had an HR of 1.64 (95%CI 1.44, 1.86) compared to those with normal BMI. Similar figures were seen in females (HR 1.48, 95%CI 1.37, 1.61). Those being overweight before age 40 had an HR of obesity-related cancers of 1.16 (95%CI 1.02, 1.32) and 1.15 (95%CI 1.04, 1.27) in males and females, respectively. Excluding postmenopausal breast cancer from the obesity-related cancers, females being overweight before age 40 had an HR of 1.27 (95%CI 1.13, 1.44).

One unit increase in BMI (HR 1.03, 95%CI 1.01, 1.05) and 5 kg increase in weight (HR 1.07, 95%CI 1.03, 1.10) were associated with increased risk of postmenopausal breast cancer (Table 4). The HR for OBY was 1.02 (95%CI 1.01, 1.03). Those being obese at

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the first two measurements had an HR of 1.22 (95%CI 1.07, 1.39), compared to those with normal BMI.

One unit increase in BMI (HR 1.10, 95%CI 1.07, 1.13) and 5 kg increase in weight (HR 1.21, 95%CI 1.15, 1.28) were associated with increased risk of endometrial cancer (Table 5). The HRs for OWY and OBY were 1.03 (95%CI 1.01, 1.05) and 1.11 (95%CI 1.09, 1.13), respectively. Those being obese at the first two measurements, overweight at first and obese at second, and those being overweight at both measurements were all at increased risk. Females being overweight before age 40 had an HR of endometrial cancer of 1.70 (95%CI 1.31, 2.22).

In males, the HR of colon cancer for OBY was 1.04 (95%CI 1.02, 1.07), and in females the HR for OWY and OBY were 1.03 (95%CI 1.01, 1.04) and 1.03 (95%CI 1.01, 1.05), respectively (Table 6). Those being obese at the first two measurements, overweight at first and obese at second, and those having normal BMI at first and overweight at second measurement were all at increased risk. Males being overweight before age 40 had an HR of 1.29 (95%CI 1.03, 1.62). For rectal cancer, those being obese at the first two measurements, were all at increased risk (Table S1).

In males, the HRs of renal cell cancer for OWY and OBY were 1.04 (95%CI 1.01, 1.07) and 1.08 (95%CI 1.04, 1.11), respectively, and in females the HR for OBY was 1.06 (95%CI 1.03, 1.09) (Table 7). Those being obese at the first two measurements were at an increased risk. Males being overweight before age 40 had an HR of 1.58 (95%CI 1.12, 2.23).

The HR of pancreatic cancer for OBY was 1.04 (95%CI 1.01, 1.08) in males (Table S2), and those being obese at the first two measurements were at increased risk (HR 1.81, 95%CI 1.22, 2.68). For ovarian cancer, no associations with the different BMI and

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weight metrics were seen (Table S3). The HR of liver cancer for OBY was 1.09 (95%CI 1.04, 1.14) in males (Table S4). Those being obese at the first two measurements and those being overweight at first and obese at second measurement were at increased risk.

Results for non-obesity-related cancers were displayed in Tables S6-S11. For cancers of the larynx, lung and trachea, inverse associations were seen for several BMI and weight metrics (Table S7), but these associations disappeared when the analysis was restricted to those who never smoked. The latter analysis, however, was based on small numbers.

Further adjustment for BMI at first measurement in the models generally had little impact on the risk estimates. However, the associations of BMI at last measurement, maximum BMI and OBY with male liver cancer and of BMI at last measurement with male renal cell cancer were weakened. Cancer-specific adjustments in sensitivity analyses within the cohorts also had minor impact on the estimates. When follow-up started one year after the health examinations, no major changes in risk were seen for obesity-related cancers overall.

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Discussion

In this large population-based study, duration of overweight (males only) and obesity over time were associated with increased risk of all obesity-related cancers combined. Being overweight before age 40 increased the risk of these cancers by approximately 15%, with higher risks particularly for endometrial, male renal cell, and male colon cancer.

Study Strengths and Limitations

Major strengths of our study were its prospective design and large size, including approximately 9,800 obesity-related cancers. We used data from population-based health examinations in Austria, Norway, and Sweden, with almost complete coverage of measured exposure factors (height and weight).[11] We also used high-quality national cancer registries for follow-up.[13-15]

The risks of postmenopausal breast and endometrial cancer associated with overweight and obesity have previously been shown to be modified by postmenopausal hormone use.[5] Although this effect modification has been similar between studies,[20;21] others have found no effect modification of the BMI-breast cancer relationship by postmenopausal hormone use.[22] Unfortunately, we had no information on postmenopausal hormone use in our data.

Although it has been suggested that other anthropometric measures than BMI (e.g. waist-to-hip ratio and waist circumference) better explain obesity-related health,[23] BMI is strongly correlated to percentage body fat within sex-age groups and may be useful for separating body fat categories at the population level.[24] It has also been argued that weight gain is a better metric than BMI change.[4] In our study, different BMI and weight metrics were constructed to capture various aspects of adult weight gain over time. These metrics

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are highly correlated, and consequently, it is difficult to separate their effects. Further, information on waist circumference or waist-to-hip ratio was not available in all cohorts, and was not used in our analyses.

BMI at first and last measurement show the results of the first and last surveys for the individuals in our study, although they were performed at different ages and calendar time. For the cancer patients, mean time between last measurement and diagnosis was 10 years (range; 0-35 years), indicating that most had their last measurement taken long time before diagnosis. We displayed results for five BMI trajectories, including 92% of the study population. Moreover, 3.6% of the study population were overweight at first measurement and had normal BMI at second, 0.1% were obese at first measurement and had normal BMI at second, and 0.4% had normal BMI at first measurement and obese at second. However, we consider these and other groups of similar size to be too small to make meaningful analyses.

The first BMI measurement above 25 indicated when an individual was overweight for the first time. Further, the length of time as overweight (OWY) or obese (OBY) were estimated based on known BMI-measurements, allowing us to take the degree of overweight and obesity for each individual over time into account. This has been a better approach for many obesity-related outcomes than cross-sectional BMI information.[25]

Since we were unable to differentiate between intentional and unintentional weight loss, the influence of comorbidities and reverse causation is a concern. However, no major changes in risk estimates were seen when follow-up started one year after the health examinations. Also the risk of the obesity-related cancers increased consistently with increasing maximum BMI in our study. This metric appears to be unaffected by disease-

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associated weight loss in studies on the mortality risk of obesity,[26] and has been used to minimize confounding by disease when weight histories are unavailable.

One of the main aims of our study was to explore the impact of BMI and weight changes over time on obesity-related cancers. Consequently, our study population was restricted to those with two or more health examinations, and we only included individuals with measurements at least three years apart. There were no major differences between basic characteristics, such as BMI at first measurement, of those with measurements from two or more surveys and those with only one measurement. Never-smokers at first examination, however, were more likely to be included than smokers (55% never-smokers among the study participants vs. 39% among those excluded).

We presented results for obesity-related cancers combined and for major obesity-related cancers according to various BMI and weight measures, which may raise concern about false positive associations. However, we only presented results for associations between BMI and weight measures and known obesity-related cancers. For comparison, however, we also showed results for non-obesity-related cancers.

Comparisons with Other Studies

For postmenopausal breast cancer, adult weight gain has consistently been positively associated with risk and strongest for estrogen and progesterone receptor positive tumors, whereas excess weight has been inversely associated with risk of premenopausal breast cancer.[9;27-30] However, it has also been suggested that short-term weight gain could increase the risk of breast cancer in premenopausal women.[8] In our study, one unit increase in BMI and 5 kg increase in weight as well as duration of obesity were associated with increased

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risk of postmenopausal breast cancer. Being overweight before age 40 did not, however, increase the risk.

Excess weight or greater BMI are key risk factors for endometrial cancer, and more than 40% of all new cancers in Northern Europe are attributable to high BMI.[31;32] Epidemiological studies suggest that obesity is associated with both main histological subtypes of endometrial cancer (type I and II), although to a lesser extent among type II.[33;34] Adult weight gain has also consistently been associated with endometrial cancer risk among women not using postmenopausal hormone therapy.[4;5] Although obesity throughout life has been positively associated with risk, adult or current obesity seem to play the most critical role.[10;35] Other studies suggest that excess weight during adolescence and young adulthood also contribute to risk.[36;37] In our study, one unit increase in BMI and 5 kg increase in weight, duration of overweight and obesity as well as overweight before age 40 were associated with increased risk.

Ovarian cancer is regarded as obesity-related,[2] and 6% of all new cancers in Northern Europe are attributable to high BMI.[31] Also adult weight gain has been associated with increased ovarian cancer risk.[4] We have previously reported on an increased ovarian cancer risk in women who were overweight or obese in adolescence or young adulthood.[38] In the present study, however, no associations were seen for the BMI and weight metrics, which may be due to the relatively high mean age at first health examination (approximately 42 years).

For colon cancer, a stronger and more consistent association with obesity has been reported in males than females.[29;39] A 2015 meta-analysis of adult weight gain and adiposity-related cancers showed that 5 kg increase in weight increased the risk of male, but

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not female colon cancer.[4] A US cohort study of postmenopausal women, however, found that longer duration of overweight and obesity were associated with colon cancer.[5] It has also been reported that weight gain from early adulthood to midlife is associated with higher colorectal cancer risk than weight gain from midlife to older ages.[40] Duration of overweight (females) and obesity (males and females) were associated with risk of colon cancer in our study, as well as overweight before age 40 (males).

For renal cell cancer, a positive dose-response relationship between BMI and risk has been reported in both genders.[41] In a 2015 meta-analysis of prospective observational studies, those with greater adult weight gain were associated with an increased risk of kidney cancer.[4] A longer overweight duration increased the risk of female kidney cancer in a longitudinal US study.[5] In our study, duration of overweight (males) and obesity (males and females) as well as overweight before age 40 (males) were associated with increased risk.

The velocity of weight gain and duration of overweight and obesity at different points during one's life course probably influence cancer risk to different degrees.[29] Excess weight in adolescence and young adulthood increases the risk of cancers linked to adult overweight and obesity.[38;42] Those being overweight before age 40 had an increased risk of all obesity-related cancer by 16% and 15% in males and females, respectively, in our study, specifically for endometrial (70%), male renal cell (58%), and male colon cancer (29%).

Obesity has a multifactorial etiology involving a complex interplay between lifestyle, environment, nutrition, genetics and epigenetic predisposition. The underlying biological mechanisms for the association between adiposity/weight gain and cancer may

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involve changes in sex hormone metabolism, insulin and IGF (insulin-like growth factor) signalling, and adipokine pathophysiology/inflammatory pathways.[43]

In summary, this study showed that adult weight gain was associated with increased risk of several major cancers. The degree, timing and duration of overweight and obesity also seemed to be important. Overweight and obesity are important modifiable risk factors for several cancers, and preventing weight gain may be an important public health strategy to reduce the cancer risk.

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Conflict of interest

None declared.

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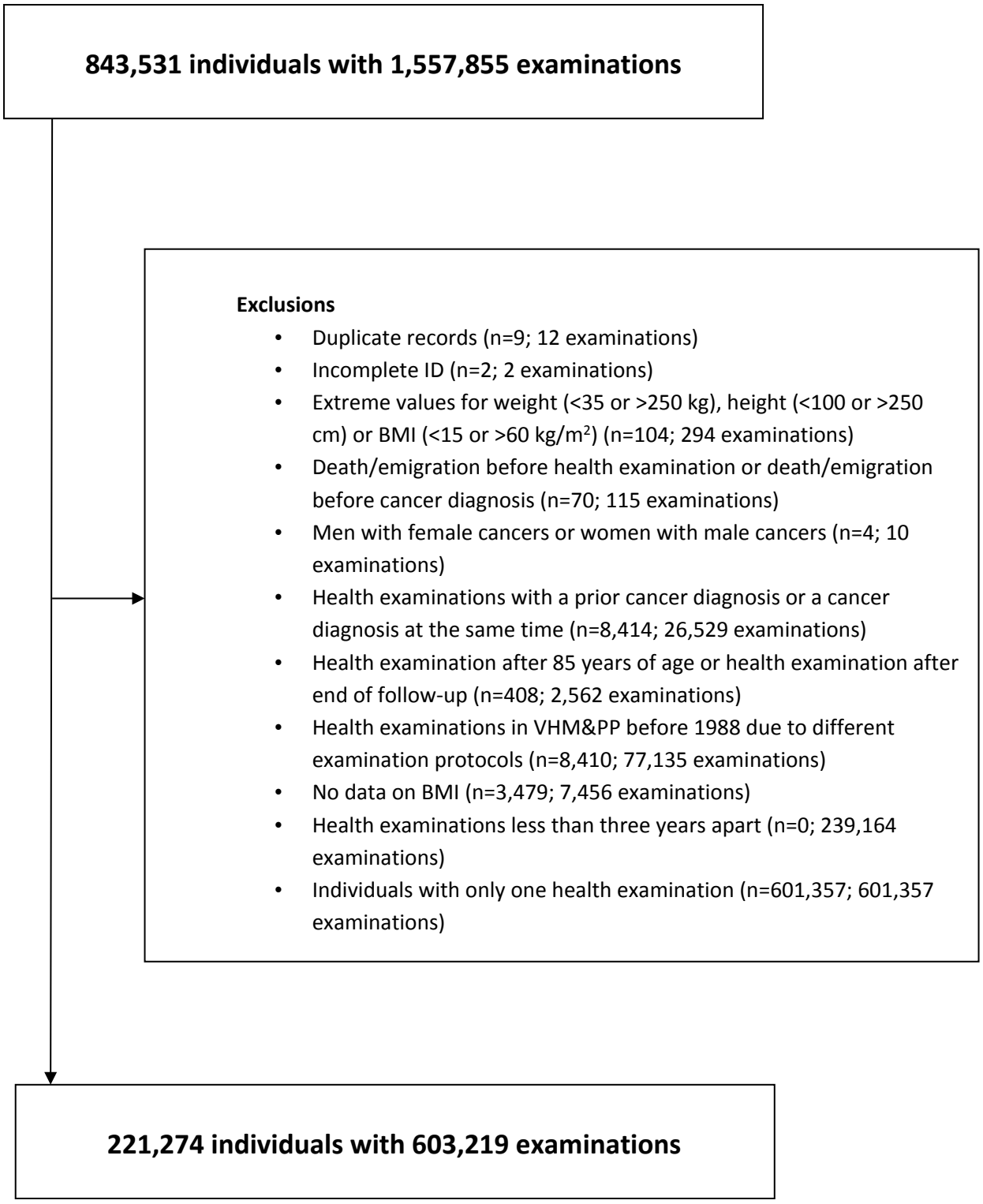
Figure 1. Selection of the study population.



BMI: Body Mass Index
VHM&PP: Vorarlberg Health Monitoring and Prevention Programme

Table 1. Characteristics of the study population at 2nd measurement

	Males		Females		Total	
	n	%	n	%	n	%
No of individuals	107,422	100.0	113,852	100.0	221,274	100.0
Country						
Austria	46,063	42.9	57,434	50.4	103,497	46.8
Norway	34,825	32.4	33,483	29.4	68,308	30.9
Sweden	26,534	24.7	22,935	20.1	49,469	22.4
Year of birth						
<1930	14,274	13.3	13,453	11.8	27,727	12.5
1930-39	25,588	23.8	24,989	21.9	50,577	22.9
1940-49	26,421	24.6	27,408	24.1	53,829	24.3
1950-59	22,477	20.9	24,883	21.9	47,360	21.4
≥1960	18,662	17.4	23,119	20.3	41,781	18.9
Age (years)						
<30	15,469	14.4	19,640	17.3	35,109	15.9
30-39	29,571	27.5	31,130	27.3	60,701	27.4
40-49	43,372	40.4	39,773	34.9	83,145	37.6
50-59	13,440	12.5	15,231	13.4	28,671	13.0
≥60	5,570	5.2	8,078	7.1	13,648	6.2
Smoking status						
Never-smoker	48,432	45.1	70,508	61.9	118,940	53.8
Ex-smoker	25,301	23.6	15,687	13.8	40,988	18.5
Smoker, packyear missing	6,248	5.8	5,201	4.6	11,449	5.2
Smoker, <5 pack-years	3,764	3.5	6,068	5.3	9,832	4.4
Smoker, 5-13.4 pack-years	7,706	7.2	8,575	7.5	16,281	7.4
Smoker, ≥13.5 pack-years	15,563	14.5	7,556	6.6	23,119	10.4
Missing	408	0.4	257	0.2	665	0.3
Height, mean (SD)	176.0	(6.8)	163.2	(6.3)	169.4	(9.2)
BMI (WHO categories, kg/m^2)						
Underweight; <18.5	431	0.4	2,626	2.3	3,057	1.4
Normal weight; 18.5-24	44,346	41.3	61,459	54.0	105,805	47.8
Overweight; 25-29	49,708	46.3	33,958	29.8	83,666	37.8
Obese; ≥30	12,937	12.0	15,809	13.9	28,746	13.0
Maximum BMI (WHO categories, kg/m^2)						
Underweight; <18.5	193	0.2	1,160	1.0	1,353	0.6
Normal weight; 18.5-24	35,573	33.1	52,459	46.1	88,032	39.8
Overweight; 25-29	54,410	50.7	38,812	34.1	93,222	42.1
Obese; ≥30	17,246	16.1	21,421	18.8	38,667	17.5
BMI-categories at first						

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two measurements						
Normal BMI at both	39,827	37.1	55,543	48.8	95,370	43.1
Normal BMI at first and overweight at second	13,488	12.6	12,349	10.8	25,837	11.7
Overweight at both	34,694	32.3	19,862	17.4	54,556	24.7
Overweight at first and obese at second	5,431	5.1	5,502	4.8	10,933	4.9
Obese at both	7,253	6.8	9,678	8.5	16,931	7.7
Other	6,729	6.3	10,918	9.6	17,647	8.0
Age at first measurement (years) **with BMI ≥25**[a]						
<40	22207	20.7	15178	13.3	37385	16.9
40-49	29785	27.7	23047	20.2	52832	23.9
≥50[b]	55430	51.6	75627	66.4	131057	59.2
Years of follow-up, mean (SD)	17.3	(8.9)	17.7	(8.7)	17.6	(8.8)

[a] Include all measurements for the individuals
[b] No BMI measurements ≥25 before age 50

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Table 2. Number of incident cancer cases

Cancer type	Males		Females		Total	
	n	%	n	%	n	%
All	16,244	100.0	11,637	100.0	27,881	100.0
Obesity-related cancers (ICD7; ICD10)	3,378	20.8	6,383	54.9	9,761	35.0
Oesophagus (adenocarc.) (150; C15)[a]	75	0.5	13	0.1	88	0.3
Gastric cardia (151.1; C16.0)	96	0.6	37	0.3	133	0.5
Colon (153; C18)	1,118	6.9	927	8.0	2,045	7.3
Rectum (154; C19-21)	708	4.4	511	4.4	1,219	4.4
Liver (155.0; C22)	176	1.1	90	0.8	266	1.0
Gallbladder (155.1-3; C23-24)	84	0.5	102	0.9	186	0.7
Pancreas (157; C25)	348	2.1	331	2.8	679	2.4
Breast (postmenopausal[b]) (170; C50)	0	0.0	2,452	21.1	2,452	8.8
Endometrium(172; C54)[a]	0	0.0	730	6.3	730	2.6
Ovary (175.0; C56)	0	0.0	450	3.9	450	1.6
Renal cell (180.0, 180.9; C64)	431	2.7	268	2.3	699	2.5
Meningioma (193; C70-72, D32–33, D42–43)[a]	54	0.3	119	1.0	173	0.6
Thyroid (194; C73)	91	0.6	169	1.5	260	0.9
Multiple myeloma (203; C90)	197	1.2	184	1.6	381	1.4
Other cancers	12,866	79.2	5,254	45.1	18,120	65.0
Larynx, lung, trachea (161-162; C32-34)	1,793	11.0	861	7.4	2,654	9.5
Melanoma (190 ; C43)	700	4.3	563	4.8	1,263	4.5
Breast (premenopausal) (170; C50)	0	0.0	1,003	8.6	1,003	3.6
Prostate (177; C61)	5,833	35.9	0	0.0	5,833	20.9
Bladder (181.0; C67; D09.0)	1,034	6.4	277	2.4	1,311	4.7

[a] Combined with morphology codes
[b] Above the age of 55 at the time of diagnosis

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Table 3. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associations of various measures of body mass index (BMI) and weight in relation to obesity-related cancer, Me-Can 2.0 study

	Males					Females				
BMI and weight measure	**Number of cases**	**HR [a]**	**95% CI**	**HR [b]**	**95% CI**	**Number of cases**	**HR [a]**	**95% CI**	**HR [b]**	**95% CI**
BMI at first measurement (kg/m^2)										
Underweight; <18.5	8	0.53	0.26,1.06			93	0.88	0.72,1.08		
Normal weight; 18.5-24	1,478	1.00	Ref.			3,294	1.00	Ref.		
Overweight; 25-29	1,532	1.16	1.08,1.25			2,003	1.13	1.07,1.20		
Obese; ≥30	360	1.51	1.34,1.70			993	1.45	1.35,1.56		
P for trend		<0.001					<0.001			
BMI at last measurement (kg/m^2)										
Underweight; <18.5	12	0.95	0.54,1.67	1.31	0.70,2.45	85	1.10	0.88,1.36	1.20	0.94,1.52
Normal weight; 18.5-24	1,168	1.00	Ref.	1.00	Ref.	2,629	1.00	Ref.	1.00	Ref.
Overweight; 25-29	1,685	1.19	1.10,1.28	1.13	1.03,1.25	2,251	1.12	1.06,1.19	1.09	1.02,1.17
Obese; ≥30	513	1.46	1.31,1.62	1.25	1.07,1.45	1,418	1.44	1.35,1.54	1.29	1.16,1.43
P for trend		<0.001		<0.001			<0.001		<0.001	
Maximum BMI (kg/m^2)										
Underweight; <18.5	5	0.79	0.33,1.90	2.17	0.52,9.10	35	0.99	0.71,1.39	1.15	0.75,1.75
Normal weight; 18.5-24	998	1.00	Ref.	1.00	Ref.	2,358	1.00	Ref.	1.00	Ref.
Overweight; 25-29	1,768	1.18	1.09,1.28	1.13	1.01,1.26	2,370	1.12	1.06,1.19	1.11	1.03,1.20
Obese; ≥30	607	1.47	1.32,1.63	1.26	1.06,1.50	1,620	1.43	1.34,1.52	1.31	1.17,1.48
P for trend		<0.001		<0.001			<0.001		<0.001	
BMI change[c]		1.00	0.98,1.02	1.01	0.99,1.03		1.02	1.01,1.03	1.02	1.01,1.04
Weight change[d]		1.00	0.97,1.04	1.02	0.98,1.05		1.05	1.02,1.07	1.05	1.03,1.08
Years as overweight/obese[e]										
OWY (overweight-years)		1.01	1.01,1.02	1.00	0.99,1.02		1.01	1.00,1.02	1.01	1.00,1.02
OBY (obesity-years)		1.04	1.03,1.05	1.01	0.99,1.03		1.04	1.03,1.05	1.02	1.01,1.03
BMI-categories at first two measurements[f]										

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Normal BMI at both	1,095	1.00	Ref.			2,612	1.00	Ref.		
Normal BMI at first and overweight at second	375	1.22	1.08,1.37			625	1.08	0.99,1.18		
Overweight at both	1,227	1.20	1.11,1.31			1,415	1.13	1.06,1.21		
Overweight at first and obese at second	167	1.43	1.21,1.68			370	1.37	1.23,1.53		
Obese at both	299	1.64	1.44,1.86			832	1.48	1.37,1.61		
Age at first measurement (years) **with BMI ≥25**[g]										
< 40	373	1.16	1.02,1.32			480	1.15	1.04,1.27		
40-49	1,081	1.11	1.03,1.20			1,610	1.19	1.12,1.26		
Total	3,378					6,383				

[a] Adjusted for age at first measurement and at baseline (continuous), country (Austria, Norway, Sweden) and smoking status (never smokers, former smokers, current smokers (divided into those with missing information on pack-years, <5, 5-13.4, ≥13.5 pack-years); [b] Additionally adjusted for BMI at first measurement; [c] BMI change (one unit increase) since first measurement; [d] Weight change (per 5 kg increase) since first measurement; [e] The HR_{OWY} and the HR_{OBY} are the HRs per years as overweight and obese, respectively; [f] The five BMI-trajectories include 92% of the study population; [g] The reference is those without measurements of BMI ≥25 at the specific age

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Table 4. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associations of various measures of body mass index (BMI) and weight in relation to postmenopausal breast cancer, Me-Can 2.0 study

BMI and weight measure	Number of cases	HR [a]	95% CI	HR [b]	95% CI
BMI at first measurement (kg/m^2)					
Underweight; <18.5	30	0.75	0.52,1.07		
Normal weight; 18.5-24	1,289	1.00	Ref.		
Overweight; 25-29	784	1.08	0.98,1.18		
Obese; ≥30	349	1.22	1.08,1.37		
P for trend		0.001			
BMI at last measurement (kg/m^2)					
Underweight; <18.5	23	0.76	0.50,1.15	0.84	0.54,1.31
Normal weight; 18.5-24	1,036	1.00	Ref.	1.00	Ref.
Overweight; 25-29	861	1.04	0.95,1.14	1.03	0.92,1.15
Obese; ≥30	532	1.27	1.15,1.42	1.27	1.08,1.49
P for trend		<0.001		0.001	
Maximum BMI (kg/m^2)					
Underweight; <18.5	8	0.60	0.30,1.20	0.70	0.31,1.58
Normal weight; 18.5-24	924	1.00	Ref.	1.00	Ref.
Overweight; 25-29	916	1.04	0.95,1.15	1.05	0.93,1.18
Obese; ≥30	604	1.25	1.13,1.39	1.27	1.05,1.52
P for trend		0.001		0.097	
BMI change[c]		1.03	1.01,1.05	1.03	1.02,1.05
Weight change[d]		1.07	1.03,1.10	1.07	1.04,1.11
Years as overweight/obese[e]					
OWY (overweight-years)		1.01	1.00,1.02	1.00	0.99,1.02
OBY (obesity-years)		1.02	1.01,1.03	1.02	1.00,1.04
BMI-categories at first two measurements[f]					
Normal BMI at both	1,025	1.00	Ref.		
Normal BMI at first and overweight at second	243	1.02	0.89,1.17		
Overweight at both	553	1.06	0.95,1.17		
Overweight at first and obese at second	144	1.25	1.05,1.49		
Obese at both	291	1.22	1.07,1.39		
Age at first measurement (years) **with BMI ≥25[g]**					
<40	138	0.92	0.77,1.11		
40-49	546	1.11	1.00,1.23		
Total	2,452				

[a] Adjusted for age at first measurement and at baseline (continuous), country (Austria, Norway, Sweden) and smoking status (never smokers, former smokers, current smokers (divided into those with missing information on pack-years, <5, 5-13.4, ≥13.5 pack-years); [b] Additionally adjusted for BMI at first measurement; [c] BMI change (one unit increase) since first measurement; [d] Weight change (per 5 kg increase) since first measurement; [e] The HR_{OWY} and the HR_{OBY} are the HRs per years as overweight and obese, respectively; [f] The five BMI-trajectories include 92% of the study population; [g] The reference is those without measurements of BMI ≥25 at the specific age

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Table 5. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associations of various measures of body mass index (BMI) and weight in relation to endometrial cancer, Me-Can 2.0 study

BMI and weight measure	Number of cases	HR [a]	95% CI	HR [b]	95% CI
BMI at first measurement (kg/m^2)					
Underweight; <18.5	6	0.54	0.24,1.20		
Normal weight; 18.5-24	331	1.00	Ref.		
Overweight; 25-29	221	1.33	1.12,1.59		
Obese; ≥30	172	2.71	2.24,3.28		
P for trend		<0.001			
BMI at last measurement (kg/m^2)					
Underweight; <18.5	6	0.87	0.39,1.97	1.12	0.47,2.72
Normal weight; 18.5-24	239	1.00	Ref.	1.00	Ref.
Overweight; 25-29	252	1.46	1.22,1.75	1.47	1.18,1.81
Obese; ≥30	233	2.81	2.34,3.38	2.31	1.72,3.10
P for trend		<0.001		<0.001	
Maximum BMI (kg/m^2)					
Underweight; <18.5	-	-	-	-	-
Normal weight; 18.5-24	225	1.00	Ref.	1.00	Ref.
Overweight; 25-29	248	1.31	1.09,1.58	1.36	1.08,1.71
Obese; ≥30	257	2.63	2.19,3.16	2.22	1.58,3.11
P for trend		<0.001		<0.001	
BMI change [c]		1.10	1.07,1.13	1.10	1.07,1.13
Weight change [d]		1.21	1.15,1.28	1.21	1.15,1.27
Years as overweight/obese [e]					
OWY (overweight-years)		1.03	1.01,1.05	1.02	0.99,1.05
OBY (obesity-years)		1.11	1.09,1.13	1.07	1.03,1.11
BMI-categories at first two measurements [f]					
Normal BMI at both	258	1.00	Ref.		
Normal BMI at first and overweight at second	67	1.18	0.90,1.55		
Overweight at both	152	1.32	1.08,1.63		
Overweight at first and obese at second	58	2.26	1.70,3.02		
Obese at both	152	2.97	2.42,3.65		
Age at first measurement (years) **with BMI ≥25** [g]					
<40	80	1.70	1.31,2.22		
40-49	230	1.60	1.35,1.90		
Total	730				

[a] Adjusted for age at first measurement and at baseline (continuous), country (Austria, Norway Sweden) and smoking status (never smokers, former smokers, current smokers (divided into those with missing information on pack-years, <5, 5-13.4, ≥13.5 pack-years); [b] Additionally adjusted for BMI at first measurement; [c] BMI change (one unit increase) since first measurement; [d] Weight change (per 5 kg increase) since first measurement; [e] The HR_{OWY} and the HR_{OBY} are the HRs per years as overweight and obese, respectively; [f] The five BMI-trajectories include 92% of the study population; [g] The reference is those without measurements of BMI ≥25 at the specific age

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Table 6. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associations of various measures of body mass index (BMI) and weight in relation to colon cancer, Me-Can 2.0 study

	Males					Females				
BMI and weight measure	**Number of cases**	**HR [a]**	**95% CI**	**HR [b]**	**95% CI**	**Number of cases**	**HR [a]**	**95% CI**	**HR [b]**	**95% CI**
BMI at first measurement (kg/m^2)										
Underweight; <18.5	2	0.40	0.10,1.60			12	0.87	0.49,1.54		
Normal weight; 18.5-24	502	1.00	Ref.			476	1.00	Ref.		
Overweight; 25-29	495	1.09	0.96,1.24			310	1.20	1.03,1.38		
Obese; ≥30	119	1.46	1.19,1.79			129	1.31	1.07,1.59		
P for trend		<0.001					<0.001			
BMI at last measurement (kg/m^2)										
Underweight; <18.5	4	0.97	0.36,2.61	1.48	0.51,4.33	15	1.41	0.84,2.37	1.64	0.92,2.94
Normal weight; 18.5-24	389	1.00	Ref.	1.00	Ref.	374	1.00	Ref.	1.00	Ref.
Overweight; 25-29	549	1.16	1.02,1.33	1.19	1.01,1.41	347	1.23	1.06,1.43	1.19	1.00,1.43
Obese; ≥30	176	1.55	1.29,1.86	1.52	1.17,1.99	191	1.42	1.19,1.70	1.37	1.05,1.80
P for trend		<0.001		<0.001			<0.001		0.030	
Maximum BMI (kg/m^2)										
Underweight; <18.5	2	0.96	0.24,3.85	-	-	6	1.24	0.55,2.78	1.72	0.55,5.35
Normal weight; 18.5-24	334	1.00	Ref.	1.00	Ref.	339	1.00	Ref.	1.00	Ref.
Overweight; 25-29	579	1.16	1.01,1.33	1.22	1.01,1.48	360	1.19	1.02,1.38	1.17	0.96,1.43
Obese; ≥30	203	1.52	1.27,1.81	1.55	1.15,2.10	222	1.42	1.19,1.69	1.44	1.06,1.96
P for trend		<0.001		<0.001			<0.001		0.026	
BMI change[c]		1.04	1.00,1.07	1.04	1.01,1.08		1.01	0.98,1.04	1.01	0.99,1.04
Weight change[d]		1.07	1.01,1.13	1.07	1.02,1.13		1.03	0.98,1.09	1.04	0.98,1.10
Years as overweight/obese[e]										
OWY (overweight-years)		1.01	1.00,1.03	1.01	0.99,1.03		1.03	1.01,1.04	1.02	1.00,1.05
OBY (obesity-years)		1.04	1.02,1.07	1.03	0.99,1.06		1.03	1.01,1.05	1.03	0.99,1.06
BMI-categories at first two measurements[f]										

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Normal BMI at both	367	1.00	Ref.			369	1.00	Ref.		
Normal BMI at first and overweight at second	134	1.31	1.07,1.60			101	1.30	1.04,1.62		
Overweight at both	395	1.14	0.98,1.31			218	1.23	1.04,1.46		
Overweight at first and obese at second	55	1.43	1.08,1.91			58	1.63	1.23,2.16		
Obese at both	100	1.63	1.30,2.04			102	1.33	1.07,1.67		
Age at first measurement (years) **with BMI ≥25**[g]										
<40	120	1.29	1.03,1.62			67	1.22	0.93,1.61		
40-49	356	1.08	0.94,1.24			257	1.21	1.04,1.41		
Total	1,118					927				

[a] Adjusted for age at first measurement and at baseline (continuous), country (Austria, Norway, Sweden) and smoking status (never smokers, former smokers, current smokers (divided into those with missing information on pack-years, <5, 5-13.4, ≥13.5 pack-years); [b] Additionally adjusted for BMI at first measurement; [c] BMI change (one unit increase) since first measurement; [d] Weight change (per 5 kg increase) since first measurement; [e] The HR_{OWY} and the HR_{OBY} are the HRs per years as overweight and obese, respectively; [f] The five BMI-trajectories include 92% of the study population; [g] The reference is those without measurements of BMI ≥25 at the specific age

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Table 7. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associations of various measures of body mass index (BMI) and weight in relation to renal cell cancer, Me-Can 2.0 study

	Males					Females				
BMI and weight measure	**Number of cases**	**HR [a]**	**95% CI**	**HR [b]**	**95% CI**	**Number of cases**	**HR [a]**	**95% CI**	**HR [b]**	**95% CI**
BMI at first measurement (kg/m^2)										
Underweight; <18.5	0	-	-			4	0.82	0.30,2.22		
Normal weight; 18.5-24	163	1.00	Ref.			136	1.00	1.00,1.00		
Overweight; 25-29	214	1.47	1.20,1.81			83	1.17	0.88,1.54		
Obese; ≥30	54	1.97	1.44,2.70			45	1.63	1.16,2.30		
P for trend		<0.001					0.001			
BMI at last measurement (kg/m^2)										
Underweight; <18.5	2	1.35	0.33,5.48	2.82	0.70,11.41	3	0.90	0.29,2.85	0.94	0.27,3.33
Normal weight; 18.5-24	132	1.00	Ref.	1.00	Ref.	102	1.00	Ref.	1.00	Ref.
Overweight; 25-29	228	1.41	1.14,1.76	1.12	0.85,1.48	101	1.34	1.01,1.77	1.36	0.98,1.90
Obese; ≥30	69	1.64	1.22,2.21	1.00	0.65,1.54	62	1.66	1.20,2.29	1.52	0.93,2.48
P for trend		<0.001		0.42			<0.001		0.005	
Maximum BMI (kg/m^2)										
Underweight; <18.5	0	-	-	-	-	2	1.38	0.34,5.60	1.99	0.28,14.19
Normal weight; 18.5-24	108	1.00	Ref.	1.00	Ref.	89	1.00	Ref.	1.00	Ref.
Overweight; 25-29	234	1.43	1.13,1.80	1.15	0.82,1.60	105	1.35	1.01,1.80	1.44	1.00,2.05
Obese; ≥30	89	1.88	1.41,2.51	1.23	0.75,2.02	72	1.71	1.24,2.35	1.66	0.95,2.89
P for trend		<0.001		0.25			<0.001		0.003	
BMI change [c]		0.99	0.94,1.04	1.00	0.95,1.05		1.05	1.00,1.11	1.05	1.00,1.11
Weight change [d]		1.00	0.91,1.09	1.02	0.94,1.11		1.10	1.00,1.22	1.11	1.01,1.22
Years as overweight/obese [e]										

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OWY (overweight-years)		1.04	1.01,1.07	1.01	0.98,1.05		1.02	0.99,1.05	1.02	0.98,1.06
OBY (obesity-years)		1.08	1.04,1.11	1.04	0.99,1.10		1.06	1.03,1.09	1.06	1.00,1.12
BMI-categories at first two measurements[f]										
Normal BMI at both	121	1.00	Ref.			109	1.00	Ref.		
Normal BMI at first and overweight at second	41	1.20	0.84,1.71			24	1.08	0.69,1.68		
Overweight at both	169	1.49	1.18,1.89			63	1.26	0.92,1.74		
Overweight at first and obese at second	29	2.16	1.44,3.26			14	1.35	0.77,2.37		
Obese at both	41	1.93	1.34,2.76			38	1.71	1.17,2.50		
Age at first measurement (years) **with BMI ≥25**[g]										
<40	61	1.58	1.12,2.23			22	1.21	0.75,1.97		
40-49	142	1.38	1.10,1.73			67	1.30	0.96,1.74		
Total	431					268				

[a] Adjusted for age at first measurement and at baseline (continuous), country (Austria, Norway, Sweden) and smoking status (never smokers, former smokers, current smokers (divided into those with missing information on pack-years, <5, 5-13.4, ≥13.5 pack-years); [b] Additionally adjusted for BMI at first measurement; [c] BMI change (one unit increase) since first measurement; [d] Weight change (per 5 kg increase) since first measurement; [e] The HR_{OWY} and the HR_{OBY} are the HRs per years as overweight and obese, respectively; [f] The five BMI-trajectories include 92% of the study population; [g] The reference is those without measurements of BMI ≥25 at the specific age

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