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Overweight, obesity and risk of haematological malignancies: A cohort study of Swedish and Finnish twins

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ABSTRACT

Background: Obesity is related to an increased risk of several forms of cancer. However, findings from studies on haematological malignancies are inconsistent.
Methods: We used prospectively collected data from two Swedish twin cohorts and the Finnish Twin Cohort (in total 70,067 persons) to study the effects of overweight and obesity on the development of leukaemia, non-Hodgkin lymphoma, Hodgkin's lymphoma and myeloma. The cohorts were followed from baseline through 2002 (Sweden) and through 2004 (Finland).
Results: We found a risk increase of myeloma with a relative risk (RR) of 2.1 (95% confidence interval [CI] 1.1–3.7) among obese persons, a RR of 2.5 (1.0–6.2) for chronic myeloid leukaemia and a RR of 2.7 (0.8–9.6) for acute lymphoblastic leukaemia among overweight persons as compared to normal-weighted ones.
Conclusions: Our results add further evidence suggesting that overweight and obesity may have an impact on some haematological malignancies, in particular myeloma.

1. Introduction

The increasing prevalence of obesity is of great concern for public health as it is known to be a major contributor to the global burden of disease.[1] The prevalence of overweight, defined as a body mass index (BMI, weight/height^2) of 25–29 kg/m^2, and obesity, BMI $\geqslant$ 30 kg/m^2, has been rapidly increasing during recent decades in both developed and developing countries.[1] In the US and Europe, obesity affects approximately 15–25% of men and 10–35% of women.[2]

Obesity is related to an increased risk of cardiovascular disease, type-2 diabetes and certain forms of cancer.[1,3] Proposed mechanisms for the effect on the risk of developing malignancy are through increased serum levels of bioavailable insulin-like growth factor-I (IGF-I), chronic hyperinsulinaemia, oestrogens and dysregulation of immune response.[4]

Several studies have investigated a possible association between obesity and haematological malignancies, most of them based on relatively small numbers of events.[5–16] Given the increasing concern about the effect of obesity on global health and the inconsistent results in previous studies, our

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a priori hypothesis is that overweight and obesity increase the risk of developing haematological malignancies in a large prospective study of combined data from well-established Swedish and Finnish cohorts of twins.

2. Materials and methods

The study base consists of two cohorts from the Swedish Twin Registry and one Finnish Twin Cohort, used as ordinary cohorts, without using the genetic data, as they have been shown to be representative of the general population of Sweden and Finland.[17,18] The *older* Swedish Twin Cohort was established 1961 when questionnaires were sent to all 25,778 individuals in a same-sexed twin pair born between 1886 and 1925 and both living in Sweden in 1961.[19] Additional questionnaires were administered in 1963, 1967 and, with fewer questions, in 1970 (response rates 81.5–85.1%). The present study includes the 19,262 individuals who responded to the 1967 questionnaire, and who were still alive and not previously diagnosed with a haematological malignancy by January 1, 1969 (baseline).

The *younger* Swedish Twin Cohort consists of all twin pairs born 1926–1967 who were alive and living in Sweden in 1970. During 1972–1973, a questionnaire was mailed to every same-sexed twin pair born between 1926 and 1958 in which both individuals were alive (response rate 83.1%).[19] In our study, the 26,640 subjects that were alive and not previously diagnosed with a haematological malignancy in March 1, 1974 (baseline) were included.

In 1974, a cohort of twins born before 1958 and alive in 1967 was compiled from the Central Population Registry of Finland. A questionnaire was sent to all pairs in 1975 with an overall response rate of 89%.[20] The Finnish Twin Cohort includes in total 25,882 adult same-sexed twins, with both cotwins alive in 1975.[17] Two follow-up questionnaires were administered in 1981 and 1990 (overall response rates 84% and 77%, respectively).[21] Our study includes all the adult same-sexed twin pairs of known zygosity, still alive and not previously diagnosed with a haematological malignancy in January 1, 1977 (baseline), in total, 24,165 persons.

Study participants' age at baseline differs considerably between the two Swedish cohorts (a median age in the older cohort of 56 years and in the younger cohort of 31 years). We decided to analyse the cohorts both combined and separately. The Finnish twins were divided into two subgroups (a younger cohort where the age range is 18–46 years and an older cohort aged 47–96 years) so as to be more comparable to the Swedish twin cohorts in reference to age distribution (Table 1). In the analyses, the older and younger Swedish and Finnish twins were combined into an older cohort and a younger cohort, respectively. The study population was restricted to individuals at least 18 years of age at baseline.

Cancer incidence, date of death and emigration were ascertained by record linkage to the National Cancer, Population and Mortality Registries. We calculated person-years from baseline until diagnosis of a haematological malignancy, death, emigration or end of the study (December 31, 2002 in Sweden and December 31, 2004 in Finland), whichever came first. In the Swedish and Finnish Cancer Registries, malignancies are coded according to the *International Classification of*

Table 1 – Descriptive data of the individuals in the older and younger twin cohorts in Sweden and Finland.

	Older twin cohort						Younger twin cohort					
	Sweden $n = 19,262$ (8401 men, 10,861 women)			Finland $n = 5842$ (2540 men, 3302 women)			Sweden $n = 26,640$ (12,650 men, 13,990 women)			Finland $n = 18,323$ (9212 men, 9111 women)		
	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Men												
Age at baseline	57	55	43–83	56	53	46–89	32	30	18–48	29	28	18–45
Years of follow-up	21	22	0–34	19	21	0–29	28	29	0–29	27	29	0–29
Height (cm)	173	173	145–196	172	172	145–193	178	178	141–203	176	176	149–201
Weight (kg)	74	74	40–162	74	74	44–130	72	72	40–130	73	72	40–125
BMI (kg/m^2)	24.8	24.5	14.8–56.7	25.2	24.9	15.6–46.1	22.9	22.7	14.0–41.5	23.5	23.2	14.5–41.3
Women												
Age at baseline	57	56	43–83	58	56	46–96	32	31	18–48	29	27	18–46
Years of follow-up	24	26	0–34	22	26	0–29	28	29	0–29	28	29	0–29
Height (cm)	162	162	142–183	159	160	142–180	164	164	140–194	163	163	140–183
Weight (kg)	64	63	40–132	65	64	40–125	58	57	40–128	58	56	40–118
BMI (kg/m^2)	24.5	24.2	14.7–52.0	25.5	25.1	15.0–50.2	21.5	20.9	14.9–53.3	21.7	21.2	14.4–42.6

Baseline for subjects in the Swedish older cohort is 1969 and for subjects in the younger cohort is 1974. For all subjects in the Finnish cohorts, the baseline is 1977. BMI = Body mass index.

Diseases, 7th revision (ICD-7), during the investigated period. In total, 731 cases of haematological malignancies were identified; 278 cases of leukaemia (ICD-7 204–207), 290 cases of non-Hodgkin lymphoma (NHL, ICD-7 200 and 202), 32 cases of Hodgkin's lymphoma (HL, ICD-7 201) and 140 cases of myeloma (ICD-7 203). The leukaemias consist of 14 cases of acute lymphoblastic leukaemia (ALL), 128 cases of chronic lymphocytic leukaemia (CLL), 66 cases of acute myeloid leukaemia (AML) and 21 cases of chronic myeloid leukaemia (CML). The effect of BMI on hormone-dependent malignancies was recently investigated in these cohorts.[22] The cancer incidence in twins does not differ from that of singletons with the possible exception of breast cancer in young adults and testis cancer.[17,18]

BMI (kg/m^2) was used as a measure of relative body weight and calculated from self-reported weight and height. The twins were requested to report their height and weight at the time they answered the questionnaire. Assessment of exposure is based primarily on the questionnaire administered at least 1 year before baseline (1967, 1972–1973 and 1975, respectively). We chose to categorise BMI according to WHO criteria to allow comparability between studies; BMI <18.5 (thinness), BMI 18.5–24.9 (normal, reference category), BMI 25.0–29.9 (overweight), BMI $\geqslant$30.0 (obesity).[1] Furthermore, analyses were made with BMI as a continuous variable presented as the relative risk per one unit change of the BMI. There were 25,104 individuals in the older cohort and 44,963 individuals in the younger cohort. The correlation between self-reported and measured BMI has been investigated in the Finnish Twin Cohort. The correlation was 0.92 in the younger age group measured on average 1 year later than the questionnaire, and 0.89 in older twins measured 3–4 years later than the 1990 questionnaire.[23]

2.1. Statistical methods

We estimated the relative risk (RR) and its 95% confidence interval (CI) of each haematological malignancy using Cox's Proportional Hazards Model, (SAS program PHREG, SAS Institute, Cary, North Carolina). To ensure that confidence intervals took into account the dependencies within twin pairs we performed analyses that adjusted variance estimates for correlated outcomes. We accomplished this through the use of a SAS macro that stems from the same theoretical background[24,25] and yields the same results as the published Fortran program of D.Y. Lin.[24] In simple terms, variance estimates are increased in magnitude proportional to the degree of extra correlation within twin pairs. Thus, adjusted confidence intervals are generally more conservative than unadjusted as the twins are generally positively correlated for traits. If correlations within twin pairs do not differ from what is observed between unrelated individuals in the cohort with respect to cancer risk, adjusted and unadjusted variance estimates are identical. Relative risk estimates are not altered by this procedure.

2.2. Confounders and effect modifiers

All analyses were adjusted for age at enrollment, sex and country. Further, we used questionnaire data to control for potential confounding from alcohol consumption (reference category up to the 3rd quartile at 213 g/month, with the upper quartile divided into two categories at 720 g/month), level of education (elementary school or less, education above elementary school), physical activity at work (sedentary, active, physically strenuous), recreational physical activity (physically inactive, intermediate activity, hard physical training), diabetes mellitus (yes/no according to self-report) and smoking habits (never-smoker, former smoker, current smoker).

3. Results

In Table 1, the characteristics of the cohorts are presented. Table 2 shows results when all cohorts were combined. The results for separate analyses of the older and younger cohorts are presented in Tables 3 and 4, respectively. With the exception of AML, there were no appreciable differences in the results between men and women. Adjustment for confound-

Table 2 – Age-, sex- and country-adjusted relative risks (RR) and 95% confidence intervals (CI) for haematological malignancies in relation to body mass index at baseline for all 70,067 Swedish and Finnish twins together.

Diagnosis (ICD-7)	Body mass index (kg/m^2)										
	$\leqslant$18.49			18.50–24.99[a]		25.00–29.99			$\geqslant$30.00		
	N_c	RR	95% CI	N_c	RR	N_c	RR	95%CI	N_c	RR	95% CI
Total number of individuals	3268			48,199		16,099			2501		
All haematological malignancies	7	0.4	0.2–0.9	455	1.0	230	1.0	0.9–1.2	39	1.2	0.9–1.7
Leukaemia (204–207)	1	0.2	0.0–1.1	175	1.0	90	1.0	0.8–1.4	12	0.9	0.5–1.7
CLL (2041)	0		–	85	1.0	36	0.8	0.5–1.2	7	1.0	0.5–2.2
Other leukaemia combined	1	0.2	0.0–1.8	90	1.0	55	1.4	1.0–2.0	5	0.8	0.3–2.1
ALL (2040)	0		–	8	1.0	6	2.7	0.8–9.6	0		–
AML (2050)	0		–	40	1.0	24	1.4	0.8–2.3	2	0.7	0.2–3.1
CML (2051)	1	3.0	0.3–28.6	9	1.0	11	2.5	1.0–6.2	0		–
NHL (200+202)	4	0.6	0.2–1.6	186	1.0	86	0.9	0.7–1.2	14	1.1	0.6–1.9
HL (201)	2	2.1	0.5–9.6	19	1.0	11	1.7	0.8–3.6	0		–
Myeloma (203)	0		–	82	1.0	45	1.0	0.7–1.5	13	2.1	1.1–3.7

N_c = No. of cases; CLL = Chronic lymphocytic leukaemia; ALL = Acute lymphoblastic leukaemia; AML = Acute myeloid leukaemia; CML = Chronic myeloid leukaemia; NHL = Non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma.
a Reference category.

Table 3 – Age-, sex- and country-adjusted relative risks (RR) and 95% confidence intervals (CI) for haematological malignancies in relation to body mass index at baseline for the older cohort; 19,262 Swedish twins followed 1969–2002 and 5842 Finnish twins followed 1976–2004.

Diagnosis (ICD-7)	Body mass index (kg/m^2)										
	⩽18.49			18.50–24.99[a]		25.00–29.99			⩾30.00		
	N_c	RR	95% CI	N_c	RR	N_c	RR	95% CI	N_c	RR	95% CI
Total number of individuals	367			13,842		9268			1627		
All haematological malignancies	2	0.4	0.1–1.5	256	1.0	176	1.1	0.9–1.3	34	1.4	0.9–2.0
Leukaemia (204–207)	1	0.4	0.1–3.2	102	1.0	73	1.1	0.8–1.5	10	1.0	0.5–1.9
CLL (2041)	0		–	55	1.0	32	0.9	0.6–1.4	6	1.1	0.5–2.6
ALL (2040)	0		–	1	1.0	2	2.8	0.2-32.8	0		–
AML (2050)	0		–	22	1.0	22	1.8	1.0–3.2	1	0.5	0.1–3.6
CML (2051)	1	9.5	1.2–78.5	5	1.0	9	2.6	0.9–7.7	0		–
NHL (200+202)	1	0.5	0.1–3.5	99	1.0	63	1.0	0.7–1.3	11	1.1	0.6–2.1
HL (201)	0		–	6	1.0	5	1.2	0.4–3.8	0		–
Myeloma (203)	0		–	54	1.0	37	1.0	0.7–1.6	13	2.5	1.4–4.7

N_c = No. of cases; CLL = Chronic lymphocytic leukaemia; ALL = Acute lymphoblastic leukaemia; AML = Acute myeloid leukaemia; CML = Chronic myeloid leukaemia; NHL = Non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma.
a Reference category.

Table 4 – Age-, sex- and country-adjusted relative risks (RR) and 95% confidence intervals (CI) for haematological malignancies in relation to body mass index at baseline for the younger cohort; 26,640 Swedish twins followed 1974–2002 and 18,323 Finnish twins followed 1976–2004.

Diagnosis (ICD-7)	Body mass index (kg/m^2)										
	⩽18.49			18.50-24.99[a]		25.00-29.99			⩾30.00		
	N_c	RR	95% CI	N_c	RR	N_c	RR	95% CI	N_c	RR	95% CI
Total number of individuals	2901			34,357		6831			874		
All haematological malignancies	5	0.5	0.2–1.2	199	1.0	54	0.9	0.7–1.3	5	0.7	0.3–1.7
Leukaemia (204–207)	0		–	73	1.0	17	0.9	0.5–1.5	2	0.8	0.2–3.2
CLL (2041)	0		–	30	1.0	4	0.4	0.2–1.2	1	0.8	0.1–5.8
ALL (2040)	0		–	7	1.0	4	3.5	0.9–12.9	0		–
AML (2050)	0		–	18	1.0	2	0.4	0.1–1.6	1	1.4	0.2-12.5
CML (2051)	0		–	4	1.0	2	3.2	0.5–21.7	0		–
NHL (200+202)	3	0.8	0.2–2.5	87	1.0	23	0.8	0.5–1.3	3	0.9	0.3–2.8
HL (201)	2	2.3	0.5-11.5	13	1.0	6	2.3	0.8–6.1	0		–
Myeloma (203)	0		–	28	1.0	8	1.0	0.4–2.3	0		–

N_c = No. of cases; CLL = Chronic lymphocytic leukaemia; ALL = Acute lymphoblastic leukaemia; AML = Acute myeloid leukaemia; CML = Chronic myeloid leukaemia; NHL = Non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma.
a Reference category.

ers did not appreciably change the relationship between BMI and cancer risk. Therefore, the presented results are only adjusted for age, sex and country.

Obesity was associated with an increased risk of myeloma, which was confined to the older cohort; the RR of myeloma in the older cohort was 2.5 (95% CI 1.4–4.7), with no increase in risk in the overweight. Elevated risks of myeloma in association with obesity were seen in both men and women and in both countries (data not shown). There were no cases of myeloma among the obese in the younger cohort.

We found an increasing risk of ALL with increasing BMI (RR=1.13, 95% CI 1.02–1.26) for all cohorts combined. Elevated risk estimates of ALL were found among overweight persons, but with wide confidence intervals (Tables 2–4).

Indications of increased risks for CML among overweight (overall RR=2.5, 95% CI 1.0–6.2) were seen both in the older and younger cohorts. A trend of increasing risk of CML with increasing BMI was observed in the analysis of continuous BMI in the younger cohort (RR=1.18, 95% CI 1.02–1.36), but not in the older cohort (RR=0.99, 95% CI 0.85–1.15).

A tendency towards an increased risk of AML was seen in the older cohort in the overweight category, which was based on a risk increase in women (RR=2.1, 95% CI 1.0–4.4, 17 exposed cases) whereas there was no influence on the risk among men (RR=1.0, 95% CI 0.3–3.3, five exposed cases) or in the younger cohort. There were no associations in the cohorts between BMI and the risk of CLL, either overall or if separated by country or by sex.

A statistically non-significant risk of 1.7 (95% CI 0.8–3.6, 11 exposed cases) was found for HL in association with overweight. There was an indication of an increased risk of HL in association with overweight in the younger cohort, but less so in the older cohort. There were no associations between BMI and the risk of NHL. We also repeated all analyses

excluding subjects with diabetes, which did not, however, materially change the results.

4. Discussion

In this cohort study of BMI and haematological malignancies the main finding was an increased risk of myeloma among obese persons. We also found indications of increased risks for ALL and CML but with wide confidence intervals. BMI did not influence the risks of all leukaemia combined, CLL or NHL.

One strength of our study is that information about BMI and potential confounding factors was collected prospectively, and is thus not subject to recall bias or differential misclassification, which may affect the results in case-control studies. The use of the National Registries, all of high validity and completeness, provided high coverage of the population, non-differential ascertainment of incident cases, minimal loss to follow-up and minimal risk of selection bias. The Swedish Twin Registry and Finnish Twin Cohort are unique resources allowing for unusually long periods of follow-up; up to 34 years.

Diagnostic practices may have changed during our long period of follow-up resulting in non-differential misclassification of outcome, especially for subgroups of haematological malignancies. There may be some non-differential misclassification of BMI due to weight changes during follow-up. This is likely to be of greater impact for the younger cohort due to assessment of BMI at a much younger age and a longer period of follow-up compared to the older cohort. Our aim was to investigate if the risk of developing haematological malignancies is larger for persons with overweight/obesity at older age compared with younger age. This is in accordance with findings on breast cancer where increased BMI at young age has been found to reduce the breast cancer risk, but to increase risk in older age groups.[2,26] In the younger cohort, we had the opportunity to study the influence of BMI at younger ages on risk of developing haematological malignancies later in life, whereas the impact of BMI on the risk at older ages is investigated in the older cohort. This estimate of BMI is closer to time of diagnosis and probably closer to the BMI during the years preceding cancer diagnosis than in the younger cohort and therefore non-differential misclassification is of less importance. Baseline starts at least 1 year after the individual response to the questionnaire in order to register an appropriate weight, i.e. not influenced by weight loss caused by a not yet diagnosed malignancy. Weight loss caused by malignancies undetected during an even longer period than 1 year could not give rise to spuriously increased risks, but would tend to reduce risk estimates. Non-differential misclassification of BMI or malignancy cannot explain elevated risks since it would dilute the risk estimates towards unity. The incidence of HL and ALL is highest at younger age, but very rare among the elderly, resulting in increased precision in the younger cohort than in the older cohort. The opposite pattern is seen for AML, CLL, CML, NHL and myeloma. The validity is not affected. Self-reported height and weight do not generally contribute importantly to errors in assessing BMI.[23,27] However, self-reported BMI is less reliable among overweight and obese people as they tend to underestimate their weight, resulting in non-differential misclassification and attenuated effect estimates.[23,28]

The proportion of obese subjects in the cohort was small, which leads to a greater statistical uncertainty in the analyses of disease risk among the obese. The alternative would have been to categorise BMI into quartiles which would, however, have compromised the comparability between studies. Analyses of the overweight category did, however, provide more statistically stable results.

The findings from previous epidemiologic research on the association of obesity with myeloma risk have been conflicting. We found an increased risk of myeloma in association with obesity in both men and women in the older cohort. Overweight did not affect the risk of myeloma, which implies that BMI must be profoundly elevated to increase this risk. Elevated risks of myeloma associated with obesity have also been described in some previous studies,[6,8,15] as well as a statistically non-significantly elevated risk,[13] while other cohort studies have not observed a clear association.[7,10,16] In one cohort study, the risk estimates were elevated among both white and black men, but not among women.[5]

Several studies have found an increased risk of developing leukaemia among obese persons.[9–11] Our results are in accordance with the cohort studies that observed no association between overweight or obesity and leukaemia overall.[7] Limited data are available concerning the influence of obesity on subtypes of leukaemia.

In contrast to our results, two previous studies of CLL have shown increased risks or tendencies to weak positive associations.[10,11] However, obesity did not affect the risk of CLL in a cohort study on older women,[9] nor in a recent, large cohort study[15] which strengthens our results.

The indications of risk increases of ALL and AML seen in our study in association with overweight could possibly be explained by random variation; a causal association is contradicted by the lack of elevated risks in the obese. There was, however, a trend of increasing risk of ALL with increasing BMI in the younger cohort. This is in accordance with the risk increase observed among obese men in a large cohort study, whereas no clear association was found among obese women.[15]

Our results are in accordance with the findings of increased risks of AML in association with overweight and obesity in most previous studies.[9–11] In one cohort study, however, risk of AML was not influenced by obesity.[15]

Our findings support a risk increase of CML in association with overweight, which is in accordance with a previous cohort study[15] and a large case-control study,[11] whereas no association was found in a large cohort study based on hospital discharge diagnosis of obesity[10] or a recent cohort study based on self-reported data.[16]

For NHL, prior results are conflicting where a few cohort studies and most of the case-control studies support elevated risks in association with excess body weight.[8] The largest cohort study found a relative risk of 1.16 (95% CI 1.01–1.32) of NHL among men, and no association in women.[15] Divergent results between men and women have been observed; increased risk of NHL in obese women (43 obese cases), but no association in men (nine exposed cases).[7] Weight at different ages was asked for in a recent case-control study, where

the risk of NHL tended to be larger for those who were obese in their 40s, which suggests that age at the time of obesity might play a role in the development of NHL.[14] A large cohort study based on hospital discharge diagnosis did not find an association between obesity and NHL.[10] Our results add further evidence to this and another cohort study that found no association between obesity and risk of NHL.[29]

Research on the relation of obesity to HL risk is scarce. Our study lends some support to a previous cohort study that found an association between obesity and HL, although only for men.[7] This is in contrast to two recent cohort studies that have observed no influence of overweight or obesity on risk of HL.[10,12]

One proposed mechanism for how obesity could affect the risk of developing malignancy is through the affect on the insulin-like growth factor (IGF) system. IGF-I can promote tumour development by inhibiting apoptosis and stimulating cell proliferation.[4] Several large cross-sectional studies have shown increasing IGF-I levels with increasing BMI, with the maximum concentrations at a BMI of about 25–27 kg/m^2, and decreasing levels of IGF-I with higher BMI.[4] However, blood levels of insulin-like growth factor binding proteins (IGFBPs) influence the bioavailability of IGF-I. Inverse relationships of cancer risk and blood levels of IGFBP-1 and IGFBP-2, which reduce the amount of bioavailable IGF-1, have been reported.[4] Other proposed mechanisms are impaired immune response and hyperinsulinaemia.[4]

In conclusion, our study lends additional support to the earlier findings that excess body weight increases the risk of some haematological malignancies, in particular myeloma, with some indications also for CML and ALL. We found no associations between BMI and risks of all leukaemia combined, CLL or NHL. The conflicting results between subgroups of haematological malignancies could be explained by differing pathogeneses for different subtypes of leukaemia, NHL, HL and myeloma, In view of the global expansion of obesity prevalence, it is of major public health importance to conclusively establish the impact of overweight and obesity on various forms of cancer, and to elucidate the biological mechanisms involved.

Conflict of interest statement

None declared.

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