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Obesity but not overweight increases the incidence and mortality of leukemia in adults: A meta-analysis of prospective cohort studies

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ABSTRACT

The main objectives of the present meta-analysis of prospective cohort studies were to evaluate the role of obesity on the incidence and mortality of leukemia in adults. Obesity was associated with a relative risk (RR) of 1.26 (95% CI 1.17–1.37; $p < 0.001$) for leukemia incidence and 1.29 (95% CI 1.11–1.49; $p = 0.001$) for mortality. Obesity was also associated with an increased incidence of acute myeloid leukemia (RR 1.53, 95% CI 1.26–1.85; $p < 0.001$), chronic lymphocytic leukemia (RR 1.17, 95% CI 1.08–1.27; $p < 0.001$), chronic myeloid leukemia (RR 1.16, 95% CI 1.04–1.30; $p = 0.007$) and acute lymphoblastic leukemia (RR 1.62, 95% CI 1.12–2.32; $p = 0.009$). The risk of incidence and mortality of leukemia in adults was consistently higher in obese men.

1. Introduction

Leukemia comprises a group of diseases characterized by the uncontrolled, malignant proliferation of mature leukocytes or their precursors in the blood and bone marrow. According to SEER data, approximately 44,000 individuals will be diagnosed with and 22,000 will die from some type of leukemia in 2011 in the United States (US) alone [1]. Despite recent advances in the understanding of the pathophysiology of leukemia, its etiology remains poorly understood. A series of potential entities, such as myelodysplastic syndromes or exposure to chemotherapy, have been described as risk factors for leukemia; however, in the large majority of cases, a specific cause will not be identified.

Overweight and obesity have emerged as potential risk factors for the development of leukemia, as seen in previous studies [2–4]. According to the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), overweight and obesity are defined by a body mass index (BMI) of 25–29.9 kg/m^2 and $\geq$30 kg/m^2, respectively [5,6]. In a recent report, the prevalence of overweight and obesity in adults older than 20 years of age in the US between 2007 and 2008 was 33.9% and 34.4%, respectively [7]. The same study also reports that the prevalence of overweight and obesity has been progressively increasing since 1999 in men and women of all ages and ethnicities [7]. Overweight and obesity have been associated with increased incidence and mortality rates of cardiovascular disease, diabetes mellitus and certain types of cancer.

The main objective of our study is to evaluate the association between BMI and incidence and mortality of leukemia in adult individuals. Secondary objectives were to evaluate the effect of sex on the incidence and mortality of leukemia in obese individuals, and to investigate the incidence of specific subtypes of leukemia according to BMI.

2. Methods

Two authors independently performed a search using Pubmed/MEDLINE through December 30, 2011. The key search was: *(obesity OR overweight OR "body mass" OR BMI OR "body weight" OR anthropometric) AND leukemia*. Additionally, the

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reference lists of each selected study and published meta-analyses were reviewed looking for missing studies. An article was considered relevant if it contained original data from a prospective cohort study reporting on the association between BMI and the incidence or mortality of leukemia in adults. Retrospective case-control and cross-sectional studies were excluded. Any discrepancies between reviewers were resolved through consensus. If there were multiple publications from the same study, the most relevant was selected using older publications to clarify methodology.

The data extraction was performed independently by at least two of the authors, and included author, year, country, source and size of the cohort, number of cases, years of follow-up, inclusion and exclusion criteria, methods of BMI and leukemia ascertainment, outcome and variables used for adjustment. For missing information, attempts were made to contact the authors of the original studies. The results of this meta-analysis are presented in accordance to the checklist proposed by the Meta-analysis Of Observational Studies group [8]. The quality of the studies was assessed independently by at least two of the authors using the Newcastle-Ottawa Scale (NOS) [9]. The NOS evaluates the quality of cohort studies using three parameters with a maximum of four points for selection, two points for comparability and three points for outcome. We assigned scores of 7–9 for high-quality studies. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article with the principal investigator.

The primary outcome measured was the maximally adjusted relative risk (RR) with 95% confidence interval (95% CI) of developing or dying from leukemia in overweight and obese individuals. In all calculations, the reference group was individuals with BMI 18.5–24.9 kg/m^2. To measure the outcome, the random-effects model was used [10], which accounts for heterogeneity between and within studies. We assessed for heterogeneity using the I^2 index [11]; values of 25%, 50% and 75% are consistent with mild, moderate and severe heterogeneity, respectively. Publication bias was addressed by the trim-and-fill method [12], which estimates the potential effect that non-published (imputed) studies might have had on the outcome. Leukemia subtypes were acute myeloid (AML), acute lymphoblastic (ALL), chronic myeloid (CML) and chronic lymphocytic leukemia (CLL). Meta-regression analyses were used to assess the linear relationship between BMI and incidence and mortality of leukemia. The value in kg/m^2 assigned to each category was the mid-point for closed categories. For open categories, we assumed lowest and highest BMI of 15 and 50 kg/m^2, respectively. All calculations and graphs were obtained with Comprehensive Meta-Analysis (Biostat Inc., New Jersey, USA).

3. Results

Our initial search rendered 1778 returns, from which a total of 16 prospective cohort studies on incidence [13–28] and 6 on mortality [21,29–33] were included (Fig. 1). The characteristics of the studies included in this meta-analysis are shown in Table 1. A total of 20,813 incident leukemia cases and 2358 leukemia deaths were identified in cohorts of approximately 11 million and 3 million individuals, respectively.

3.1. Incidence

Complete incidence results are shown in Table 2. Publication bias did not alter our results in any of the subsets studied.

The overall RR of leukemia for obese individuals was 1.26 (95% CI 1.17–1.37; $p < 0.001$). Meta-regression showed a 1.7% increase in leukemia incidence per kg/m^2 of BMI ($p < 0.001$). In obese men and women, there was an increased RR of leukemia (Fig. 2) but not in overweight men or women. Meta-regression showed a 2.4%

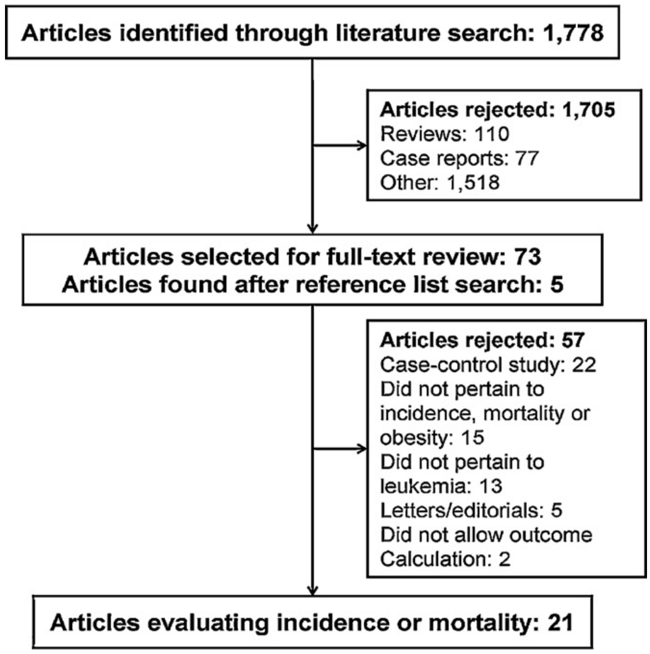


Fig. 1. Search results.

increase in the incidence of leukemia per kg/m^2 of BMI in men ($p < 0.001$) but there was no association in women ($p = 0.11$). Sensitivity analyses performed by region of report showed consistency among Asian, European and American populations with RR of 2.52 (95% CI 1.03–6.20; $p = 0.01$; $I^2 = 0\%$), 1.35 (1.16–1.55; $p < 0.001$; $I^2 = 61\%$) and 1.19 (95% CI 1.10–1.28; $p < 0.001$; $I^2 = 0\%$), respectively.

Ten studies reported on the incidence of CLL [13–15,17,20,22–25,27]. The RR of CLL was increased in obese and overweight individuals ($p < 0.001$ and $p = 0.002$, respectively). Meta-regression showed a 0.8% increase in incidence per kg/m^2 of BMI ($p = 0.07$). A significant increased incidence was found only in obese men ($p = 0.02$; Fig. 3, top). Meta-regression showed an increase of 1.3% per kg/m^2 of BMI in men ($p = 0.02$) but no linear association was found in women ($p = 0.65$).

Seven studies reported on the association between AML and BMI [14–16,22–25]. The RR of AML was statistically significant in obese individuals ($p < 0.001$). Meta-regression showed a 3.1% increase in AML incidence per kg/m^2 of BMI ($p < 0.001$). The RR of AML in obese men was 1.64 ($p < 0.001$; Fig. 3, bottom). Meta-regression showed a 3.8% increase in AML incidence per kg/m^2 of BMI in men ($p < 0.001$) but no linear relationship was found in women ($p = 0.56$).

Five studies reported on the incidence of CML [15,16,23–25]. The overall RR of CML in obese individuals was increased ($p = 0.007$), but not in overweight individuals. There was not a statistically significant association when evaluating men and women separately. Meta-regression did not show an association between BMI and CML in men or women.

Four studies reported on the incidence of ALL [15,16,23,24]. The RR for ALL was elevated in obese and overweight individuals ($p = 0.009$ and $p = 0.02$, respectively). The RR of ALL in was increased in obese men ($p = 0.03$) but not in obese women. Meta-regression analyses did not show a linear relationship between BMI and ALL in men or women.

3.2. Mortality

Six studies evaluated the association between BMI and leukemia mortality [21,29–33]. The RR for overweight and obese individuals was 1.10 (95% CI 1.00–1.21; $p = 0.05$; $I^2 = 17\%$) and 1.29 (95%

Table 1
Main characteristics of cohort studies evaluating the association between body mass index and the incidence or mortality of leukemia.

Author (year)	Country	Source of cohort	Leukemia ascertainment	BMI ascertainment	Follow-up duration (enrollment period)	Total cohort (number of cases)	Adjustments	NOS
Moller (1994) [18]	Denmark	Danish Hospital Discharge Registry, Danish Cancer, Death Registries	Danish Cancer Registry	Physical appearance	5 years (1977–1987)	43,965 (51 incident cases)	Not specified	6
Wolk (2001) [28]	Sweden	Sweden National Board of Health and Welfare Inpatient Register	Register of Causes of Death, Register of the Total Population	Physical appearance (validated in a subpopulation)	10 years (1965–1993)	28,129 (39 incident cases)	Not specified	8
Calle (2003) [30]	USA	Cancer Prevention Study II	Self-report and National Death Index	Self-reported height and weight	16 years (1982)	900,053 (1414 deaths)	Age, education, smoking, physical activity, alcohol use, marital status, race, aspirin use, fat and vegetable consumption	8
Ross (2004) [22]	USA	Iowa Women's Health Study	Iowa Cancer Registry	Self-reported height and weight	14 years (1986–2001)	37,627 (200 incident cases)	Age, exercise	8
Samanic (2004) [24]	USA	Veterans Administration Discharge Records	ICD Malignancy Coding	ICD obesity coding	12 years (1969–1996)	4,500,700 (9790 incident cases)	Age, race, calendar year	9
Batty (2005) [29]	UK	Whitehall study	National Health Service Central Registry	Measured height and weight	30 years (1967–1970)	18,403 (108 deaths)	Age, employment, physical activity, marital status, blood pressure, cholesterol, diabetes	9
Oh (2005) [19]	Korea	Korea National Health Insurance Corporation	Korea Central Cancer Registry, Korea National Health Insurance Corporation	Measured height and weight	10 years (1992–2001)	781,283 (200 incident cases)	Age, smoking, alcohol intake, family history of cancer, exercise, residence	8
Chiu (2006) [31]	USA	Chicago Heart Association cohort	State Departments of Health and National Death Index	Measured height and weight	31 years (1967–1973)	39,552 (151 deaths)	Age, race, smoking	9
Samanic (2006) [23]	Sweden	Swedish Foundation for Occupational and Health of the Construction Industry	Swedish Cancer Registry, Swedish Mortality Registry, Swedish Migration Registry	Measured height and weight	19 years (1971–1999)	362,552 (767 incident cases)	Age, calendar year, smoking status	8
Engeland (2007) [15]	Norway	Norwegian Nationwide Screening Program	Death Registry at Statistics Norway, Cancer Registry of Norway	Measured height and weight	23 years (1963–2001)	2,000,424 (6564 incident cases)	Age, year of birth	9
Fernberg (2007) [16]	Sweden	Swedish Construction Industry's Organization	Swedish Cancer, Death, Migration Registries	Self-reported height and weight	23 years (1969–1992)	336,381 (372 incident cases)	Age, smoking	8
Reeves (2007) [21]	UK	England and Scotland Breast Cancer Screening Centers	National Health Service central registers	Measured Height and Weight	5 years (1996–2005)	1,222,630 (635 incident cases, 428 deaths)	Age, region, socioeconomic status, reproductive history, smoking, alcohol, activity	7

Britton (2008) [13]	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort	Population Cancer Registries or Active Follow Up	Measured height and weight	9 years (1993 –1998)	371,983 (220 incident cases)	Age, study center, smoking, education	9
Song (2008) [26]	Korea	Korea Medical Insurance Corporation	Self Report, Korea Central Cancer Registry	Measured height and weight	10 years (1993 –1994)	170,481 (93 incident cases)	Age, height, smoking, alcohol, exercise, pay level	8
Soderberg (2008) [25]	Sweden, Finland	Sweden Twin Registry, Finnish Twin Registry	National Cancer, Population, and Mortality Registries	Self-reported height and weight	23 years (1961–2002 Sweden, 1975–2004 Finland)	70,067 (278 incident cases)	Age, sex, country, alcohol intake, education, smoking, diabetes, exercise	7
Lu (2009) [17]	USA	California Teachers Study	California Cancer Registry	Self-reported height and weight	11 years (1995 –2007)	121,216 (124 incident cases)	Height, age at menarchy, activity	7
Pylypchuk (2009) [20]	Netherlands	Netherlands Cohort Study on Diet and Cancer	Netherlands Cancer, Pathology Registry	Self-reported height and weight	13 years (1986)	120,852 (171 incident cases)	Age, sex	8
De Roos (2010) [14]	USA	Women's Health Initiative Observational Study	Self Reported with confirmation through chart review	Measured height and weight	10 years (1994 –1998)	81,219 (180 incident cases)	Age, race, education, region, smoking	9
Parr (2010) [33]	Asia-Pacific	Asia-Pacific Cohort Studies Collaboration	Summary reports and ICD codes	Self-reported height and weight	4 years (1961 –1999)	424,519 (184 deaths)	Age, smoking	8
Tsai (2010) [27]	USA	NIH-AARP Diet and Health Study, PLCO cancer screening trial	State Cancer Registries, self report with study center confirmation	Self-reported height and weight	11 years (Not specified)	525,982 (1129 incident cases)	Age, sex	7
Chu (2011) [32]	Taiwan	MJ Health Screening program	National death registry database	Self-reported height and weight	7 years (1997 –2007)	383,956 (73 deaths)	Age, sex, education, smoking, alcohol use, physical activity, clinic location	8

BMI, body mass index; NOS, Newcastle-Ottawa scale.

Table 2
Outcome estimates on the association between overweight/obesity and the incidence of leukemia subtypes according to sex.

	Overweight RR (95% CI)	*p*-Value	I^2 index	Obesity RR (95% CI)	*p*-Value	I^2 index
Leukemia						
All cases	1.09 (1.04–1.14)	<0.001	0%	1.26 (1.17–1.37)	<0.001	43%
Men	1.05 (0.99–1.13)	0.12	0%	1.40 (1.24–1.57)	<0.001	33%
Women	1.12 (1.00–1.25)	0.05	24%	1.20 (1.07–1.35)	0.002	29%
CLL						
All cases	1.10 (1.03–1.17)	0.004	0%	1.17 (1.08–1.27)	<0.001	11%
Men	1.07 (0.97–1.17)	0.17	0%	1.22 (1.04–1.45)	0.02	48%
Women	1.12 (0.96–1.31)	0.15	11%	1.09 (0.94–1.26)	0.26	0%
AML						
All cases	1.15 (0.95–1.39)	0.15	58%	1.53 (1.26–1.85)	<0.001	50%
Men	1.02 (0.85–1.22)	0.83	38%	1.64 (1.30–2.07)	<0.001	55%
Women	UTC	–	–	1.48 (1.00–2.20)	0.05	48%
CML						
All cases	1.08 (0.91–1.28)	0.39	57%	1.16 (1.04–1.30)	0.007	0%
Men	0.92 (0.59–1.44)	0.72	73%	1.16 (0.99–1.35)	0.06	0%
Women	UTC	–	–	1.17 (1.00–1.36)	0.05	0%
ALL						
All cases	1.36 (1.06–1.76)	0.02	0%	1.62 (1.13–2.32)	0.009	20%
Men	UTC	–	–	1.69 (1.04–2.73)	0.03	29%
Women	UTC	–	–	1.09 (0.38–3.07)	0.88	32%

RR, relative risk; CI, confidence interval; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia; UTC, unable to calculate.

CI 1.11–1.49; $p = 0.001$; $I^2 = 30\%$; Fig. 4), respectively. The RR for obese men was 1.45 (95% CI 1.22–1.72; $p < 0.001$; $I^2 = 0\%$) and for obese women was 1.14 (95% CI 0.99–1.33; $p = 0.07$; $I^2 = 0\%$). Meta-regression analysis showed a 1.2% increase in leukemia mortality per kg/m^2 of BMI in women ($p = 0.01$) and a 1.9% increase in men ($p = 0.10$).

4. Discussion

Based on the results of this meta-analysis, obesity but not overweight was associated with an increased incidence and mortality of leukemia in adults. Obesity was also associated with an increased incidence of every leukemia subtype. Furthermore, obese individuals consistently had a higher risk than overweight individuals, and obese men had consistently higher incidence and mortality than obese women. Finally, there was a statistically significant direct linear relationship between BMI and the incidence of AML and CLL among men.

The association of BMI and leukemia incidence found in our study is consistent with previous studies [34,35], but the association with leukemia mortality has not been previously evaluated using a meta-analytical methodology. A previous meta-analysis evaluating 9 prospective cohort studies identified a similar incidence risk of leukemia in obese individuals as the one reported

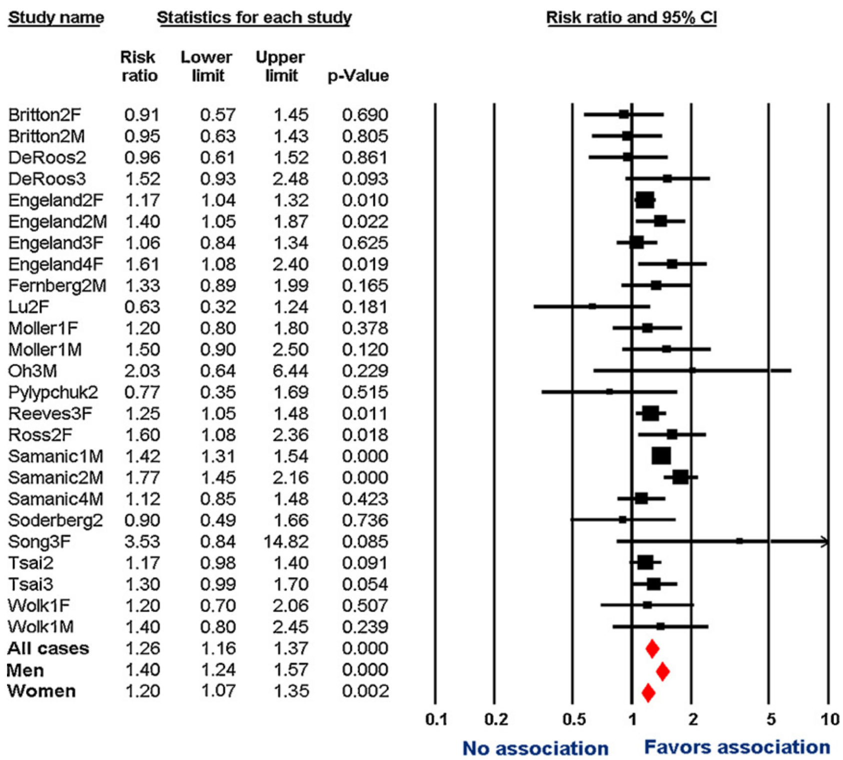
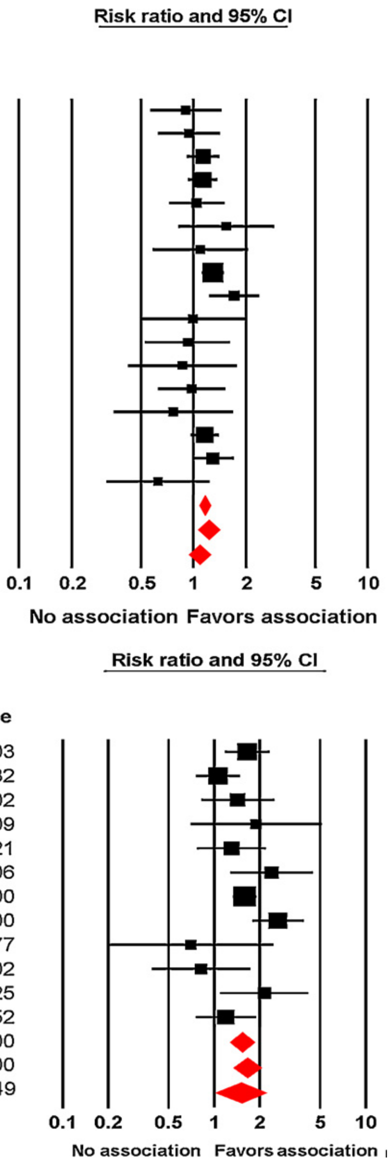


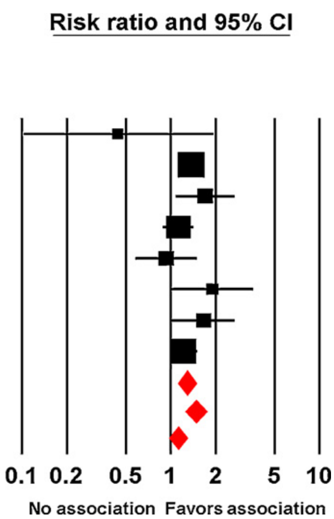
Fig. 2. Estimates of the relative risk leukemia incidence in general in obese individuals.



Study name	Risk ratio	Lower limit	Upper limit	p-Value
Britton2F	0.91	0.57	1.45	0.690
Britton2M	0.95	0.63	1.43	0.805
Engeland2M	1.14	0.92	1.41	0.221
Engeland2F	1.14	0.94	1.38	0.173
Engeland3F	1.05	0.73	1.51	0.792
Engeland4F	1.55	0.83	2.90	0.171
Ross2F	1.10	0.59	2.06	0.766
Samanic1M	1.30	1.13	1.49	0.000
Samanic2M	1.72	1.24	2.39	0.001
Soderberg2	1.00	0.50	2.00	1.000
DeRoos2	0.93	0.53	1.62	0.798
DeRoos3	0.87	0.43	1.78	0.702
Samanic4M	0.98	0.63	1.52	0.928
Pylypchuk2	0.77	0.35	1.69	0.515
Tsai2	1.17	0.98	1.40	0.091
Tsai3	1.30	0.99	1.70	0.054
Lu2F	0.63	0.32	1.24	0.181
All cases	1.17	1.08	1.27	0.000
Men	1.23	1.04	1.45	0.015
Women	1.09	0.94	1.26	0.259

Study name	Risk ratio	Lower limit	Upper limit	p-Value
Engeland2M	1.65	1.18	2.31	0.003
Engeland2F	1.06	0.76	1.48	0.732
Engeland3F	1.43	0.83	2.48	0.202
Engeland4F	1.89	0.70	5.10	0.209
Fernberg2M	1.30	0.77	2.18	0.321
Ross2F	2.40	1.29	4.47	0.006
Samanic1M	1.59	1.33	1.90	0.000
Samanic2M	2.64	1.81	3.86	0.000
Soderberg2	0.70	0.20	2.45	0.577
DeRoos2	0.82	0.39	1.73	0.602
DeRoos3	2.14	1.10	4.16	0.025
Samanic4M	1.19	0.76	1.87	0.452
All cases	1.53	1.26	1.85	0.000
Men	1.64	1.30	2.07	0.000
Women	1.48	1.00	2.20	0.049

Fig. 3. Estimates of the relative risk of acute myeloid leukemia (top) and chronic lymphocytic leukemia (bottom) incidence in obese individuals.



Study name	Risk ratio	Lower limit	Upper limit	p-Value
Batty2	0.44	0.10	1.92	0.275
Calle2	1.37	1.13	1.67	0.002
Calle3	1.70	1.08	2.67	0.021
Calle5	1.12	0.89	1.41	0.342
Calle6	0.93	0.58	1.49	0.763
Chiu2	1.90	1.02	3.53	0.043
Parr2	1.66	1.03	2.68	0.038
Reeves3	1.21	0.98	1.49	0.075
All cases	1.29	1.11	1.49	0.001
Men	1.45	1.22	1.72	0.000
Women	1.14	0.99	1.32	0.077

Fig. 4. Estimates of the relative risk of leukemia mortality in obese individuals.

here [34]. However, in such study analyses by sex and geographical region were not performed. Several aspects speak in favor of an epidemiological association between leukemia and BMI. First, obese individuals had higher risk than overweight individuals in the categorical analysis. Second, this association was confirmed in the meta-regressional analysis, showing internal validity. Finally, the large number of cases studied makes our results reliable.

Our study also showed an association between obesity and the incidence of all leukemia subtypes. Our findings are consistent with the results of a previous meta-analysis [34]. However, in our study we have additionally performed meta-regression analyses by leukemia subtype, and we found a statistically significant linear association between increasing BMI and incidence of AML, and a statistical trend for CLL. Given the large number of AML and CLL cases, it is likely our results are due to a real association between these leukemia subtypes and BMI. There also appear to be a higher incidence of CML and ALL in obese individuals, although meta-regression analyses did not reach significance. However, the number of patients included for CML and ALL was smaller. Hence, our negative results could have been due to a true lack of association or failure to identify a direct association due to the small sample size.

An important finding was the consistent elevation in the risk of leukemia incidence and mortality in obese men. These results could be partially explained by an increased incidence and mortality rates of leukemia in men compared to women. According to SEER data [1], the age-adjusted incidence and mortality of leukemia in men in the US is 16 and 10 per 100,000 while in women is 10 and 5 per 100,000, respectively. Similar rates in men are seen in the US and in Europe when evaluating the most common leukemia subtypes such as AML, CLL, CML and ALL [1,36]. On the other hand, a large US population-based study showed the prevalence rates of overweight and obesity were similar between men and women [7]. Hence, the higher risk of leukemia seen in obese but not in overweight men likely represents a biological difference between overweight and obesity additional to the inherent higher risk in men of developing leukemia. It is also likely that the increased risk of leukemia in obese men could be secondary to other behavioral factors associated with obesity specifically in men.

Our study carries inherent weaknesses. First, half of the studies evaluated BMI as a result of self-reported height and weight. However, as there is mounting data showing that is more likely for overweight individuals to report normal weights than the opposite [37], the actual association between BMI and leukemia could have been stronger than the one reported here. Second, there are several potential confounding behavioral risk factors for the development and mortality of leukemia associated with obesity that were not accounted for, such as smoking, alcohol intake, dietary factors and diabetes. Third, it is possible that other not evaluated characteristics such as increased waist-to-hip ratio, BMI at a specific age or changes in BMI over time could also be of importance. Fourth, subgroup analyses could have been affected by small sample size. Finally, our results could have been affected by ecological bias, in which individual characteristics are inferred based on the characteristics of the group to which the individual belongs but may not necessarily apply to each individual [38]. In our study, we have used standard and clinically relevant categories of BMI, and the association found in categorical and regressional analyses was consistent, adding to the validity of our results. Although the presence of ecological bias could be evaluated by performing individual-level analyses [39], such analyses are not free of shortcomings [40].

Obesity is a chronic inflammatory condition, characterized by increased production of pro-inflammatory cytokines (e.g. IL-6) and adipocytokines (e.g. adiponectin, leptin), hyperinsulinemia, insulin resistance and elevated levels of insulin-like growth factors [41,42]. All these factors have been pre-clinically associated with abnormalities in hematopoietic cell proliferation, differentiation and apoptosis [43,44]. Additionally, fat tissue adipocytes play a role in inflammation by activating T-cells and macrophages further promoting a local inflammatory state within the bone marrow microenvironment [42,45]. There is mounting evidence showing the important role the bone marrow microenvironment (i.e. adipocytes, endothelial cells, osteoblasts and osteoclasts) plays in the initiation and maintenance of hematological malignancies [46]. Hence, the relationship between obesity and leukemia is biologically plausible. However, the actual mechanisms by which obesity increase the incidence and mortality of leukemia are still to be defined.

5. Conclusions

The results of our meta-analysis showed an association between increasing BMI, specifically obesity, and the risk of developing and dying from leukemia. The risk of leukemia incidence and mortality appears consistently elevated in obese men. Maintaining a healthy body weight will positively impact public health and should be advised globally, and based on our results, could be protective against the development of leukemia. Additional studies are needed to clarify the pathophysiologic mechanisms by which obesity induce leukemia.

Conflict of interest

The authors have no conflict of interest to disclose.

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Contributions. J.J.C. designed the study; J.J.C., J.L.R. and R.R.I. performed the literature search; J.L.R., R.R.I., M.F., S.D., B.M., S.N. and A.Z. performed data gathering and quality assessment; J.J.C. performed the statistical analysis; J.J.C. and J.M. analyzed and interpreted the data. All authors wrote and approved the manuscript.

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