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Obesity over the Life Course and Risk of Acute Myeloid Leukemia and Myelodysplastic Syndromes

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Abstract

Background—Overweight and obesity are known risk factors for a number of cancers, with recent evidence suggesting that risk of hematologic cancer is also increased in obese individuals. We evaluated associations between body mass index (BMI) at differing time points during the life course in population-based case control studies of acute myeloid leukemia (AML) and myelodysplatic syndromes (MDS).

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Conflicts of Interest: None

Author Contributions

JNP and JAR conceived the project; CKB and JRC contributed to the design of the project. MAR, BH, PN, AC, and EW obtained the data and conducted central review. MR performed the data analysis; JNP provided oversight of the data analysis. JNP drafted the manuscript. All authors read and approved the final manuscript.

Methods—Cases were identified by the Minnesota Cancer Surveillance System. Controls were identified through the Minnesota State driver's license/identification card list. BMI was calculated using self-reported height and weight at ages 18, 35, and 50 years and two years prior to interview, and categorized as normal (18.5–25 kg/m^2), overweight (25–29.9 kg/m^2), obese class I (30–34.9 kg/m^2), and obese class II/III (35+ kg/m^2). All analyses were stratified by sex. Unconditional logistic regression was used to calculate odds ratios and 95% confidence intervals.

Results—We included 420 AML cases, 265 MDS cases and 1388 controls. Obesity two years prior to diagnosis was associated with AML in both males and females (OR=2.22, 95% CI 1.28, 3.85 and OR=1.85, 95% CI 1.08, 3.15 for BMI ≥ 35 vs. BMI 18.5–24.9, respectively). In contrast, associations between obesity and MDS were observed only in females. Weight change in adulthood was not consistently associated with either outcome.

Conclusion—Our results extend the emerging literature suggesting that obesity is a risk factor for hematologic malignancy and provide evidence that that the association remains regardless of timing of obesity. Obesity in adulthood is a modifiable risk factor for both MDS and AML.

Keywords

Myelodysplastic syndromes; AML; epidemiology; obesity

Introduction

Myelodysplastic syndromes (MDS) are a group of clonal hematologic disorders that result in dysplastic and ineffective hematopoiesis [1]. Individuals with MDS have a high risk of progressing to leukemia, with approximately 30% expected to develop acute myeloid leukemia (AML) [2]. MDS became reportable to the SEER Program as a hematologic malignancy in 2001. Current data suggest that the incidence rates are 4.6 per 100,000 across all age groups in the United States [3], although several studies indicate that the true rate may be higher [4]. Incidence of MDS rises with age, with the majority of cases diagnosed after age 60 years [5, 6]. General survival outcomes without intervention are poor, with 5 year relative survival estimates well below 50%[3], suggesting that prevention could have a large impact.

In the United States, 20,830 incident cases and 10,460 deaths are expected to occur in 2015 due to AML [7]. Known risk factors for AML, including ionizing radiation, smoking, exposure to benzene and other chemicals, and prior chemotherapy, explain only a small number of cases [8]. Incidence rates are higher in men than women (5.7 per 100,000 vs. 3.8 per 100,000 for all ages in the years 2001–2011) [3], although the reason is not known. Similar to MDS, survival is also poor for AML, with 5 year relative survival estimates ~30% for both males and females[3].

Overweight and obesity are known risk factors for a number of cancers [9], with recent evidence suggesting that leukemia risk is also increased in obese individuals. The majority of studies have shown a modest, but statistically significant association between obesity and leukemia, with a recent meta-analysis of prospective studies yielding an adjusted relative risk (RR) for AML of 1.53 (95% confidence interval (CI) 1.26–1.85) for individuals with a

BMI > 30.0 kg/m^2 compared to individuals with a BMI < 24.9 kg/m^2 [10]. Recent analyses from two cohorts, the NIH-AARP cohort and the Million Women Study, have also implicated overweight and obesity as risk factors for MDS [11, 12]. While the biological mechanism responsible for this increased risk is not currently known, alterations in the metabolism of endogenous hormones such as sex steroids, insulin, insulin-like growth factors, leptin and adiponectin have been hypothesized [13–18]. Even a modest increase in risk associated with obesity could have large public health implications given the high prevalence of overweight and obesity in the United States (72% males and 66% females) [19] and worldwide (37% males and 38% females) [20].

While the etiology is not well understood for either MDS or AML, the progression of MDS to AML in a substantial percentage of cases suggests that the two disorders have overlapping etiology. We evaluated the association between overweight and obesity and myeloid disorders using data from two similarly conducted population based case-control studies of AML and MDS conducted in Minnesota. The timing of overweight and obesity and weight gain in adulthood have been shown to be important for other adult cancers [21–23] but has not been explored in most previous studies of hematologic cancers. Here, we evaluated weight at multiple time points during adulthood and weight change during adulthood in addition to obesity two years prior to diagnosis.

Material and Methods

Case Ascertainment

Cases for both studies were identified by the Minnesota Cancer Surveillance System (MCSS), which is a population-based registry that collects information on all cancers diagnosed in Minnesota, using a rapid case ascertainment system. Pathology logs were typically received and reviewed by MCSS staff within 1–2 months of diagnosis. Cases were eligible for the study if they were a Minnesota resident, diagnosed between the ages of 20 and 79 years (up to 85 years for MDS), and could understand English or Spanish. Proxy interviews were not conducted.

AML Study

Detailed information regarding case and control recruitment and response rates has been described [24]. In this analysis, we included eligible cases who were diagnosed with AML (ICD-O-3 codes: 9840, 9861, 9866–9867, 9871–9874, 9891–9897, 9910, 9920) between June 1, 2005 and November 30, 2009. Centralized pathology and cytogenetics review were conducted to confirm the classification as AML. Of the 907 patients (all subtypes of myeloid leukemia) referred to the study, 58% completed the study.

MDS Study

Cases were eligible for the study if they had a diagnosis of MDS (ICD-O-3 codes: 9980, 9982–9987, 9989) between April 1, 2010 and October 31, 2014. Centralized pathology and cytogenetics review were conducted to confirm diagnosis and classify by subtypes. Only cases with confirmed MDS following review by two pathologists, a cytogeneticist and a medical oncologist were included in the analysis. Fifty-nine percent of patients referred to

the study completed the interview. This analysis is based on an interim dataset of 265 cases deemed to have true MDS following centralized pathology review.

Control Recruitment

For both studies, controls were identified through the Minnesota State driver's license/identification card list and were eligible if they were alive at the time of contact, resided in Minnesota, were between the ages of 20 and 80 years (up to 85 years for MDS controls), could understand English or Spanish, and had no prior diagnosis of myeloid leukemia. Controls were frequency matched to cases on decile of age. For the leukemia study, 701 controls were recruited (response rate 64%). For the MDS study, a total of 698 controls were recruited (interim response rate 49%). Since the same recruitment protocol and risk factor questionnaire were used, the control groups from both studies were combined to improve precision of the estimates.

This study was approved by the Institutional Review Boards of the University of Minnesota, the Mayo Clinic, the Minnesota Department of Health and participating area hospitals.

Exposure Assessment

Exposure data were collected by a self-administered questionnaire that included demographics, anthropometrics, lifestyle factors, physical activity, medication use, medical history, reproductive history, family cancer history, farm/rural living, pesticide exposure, occupational exposures, and residential chemical exposures. BMI was calculated using self-reported height and weight at age 18, 35, and 50 years, two years prior to interview, and maximum adult weight (kilograms per square meter). For analyses of BMI at age 18, we stratified the data into five categories: < 18.5 kg/m^2, 18.5–21.9 kg/m^2, 22.0–24.9 kg/m^2, 25.0–29.9 kg/m^2, and ≥ 30.0 kg/m^2. For all other ages, BMI was categorized as normal (18.5–25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), obese class I (BMI 30–34.9 kg/m^2), and obese class II/III (35+ kg/m^2). Individuals who were underweight based on WHO categories (BMI < 18.5 kg/m^2) were excluded from the analysis for ages > 18 years due to small numbers (N=23 at age 35 years, 9 at age 50 years, 19 two years prior to interview, and 2 at age of maximum BMI). Inclusion of these cases had minimal impact on the results. Change in adult weight was evaluated by calculating the amount of weight gained or lost per year between the ages of 18–35 years, age 18 years and the time of interview, and age 35 years and the time of interview. Weight changes were categorized as weight loss > 0.1 kg per year, stable weight (± 0.1 kg per year), or weight gain (0.1–0.5 kg per year, 0.5–1.0 kg per year, > 1 kg per year). Potential confounders included race/ethnicity (non-Hispanic white, other), education (≤ high school, some post high school training, college graduate), household income (≤ $40,000, > $40,000 – $80,000, > $80,000), smoking status (never, former, current), occupational and recreational physical activity, NSAID use (yes, no), personal and family history of cancer (yes, no), prior cancer treatment (yes, no), benzene exposure (yes, no), and reproductive history (number live births).

Statistical Analysis

Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed to evaluate associations between myeloid leukemia or MDS and categorical variables.

Analyses were adjusted for age and stratified by sex. Potential confounders were included in the final models if they changed the parameter estimate for the association between BMI and myeloid neoplasms more than 10%. All analyses were performed using SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA) and all reported p-values are two-sided.

Results

Selected characteristics of the combined control group and the MDS and AML cases are shown in Table 1. As expected given the higher incidence rates, there were more male cases than female cases for both AML and MDS. The majority of the cases and controls were non-Hispanic white. The majority of the MDS cases were over the age of 60 while the AML cases were more evenly distributed across the 10 year age categories. There were no significant differences in education or household income when the male and female cases were compared with their respective control groups. Current smoking was positively associated with AML in males while former smoking was associated with MDS in females.

Obesity was associated with a significant increase in risk of MDS in females but not in males (Table 2). Compared to BMI of 18.5–24.9 kg/m^2, we observed a statistically significant association between class II/III obesity (BMI ≥ 35) and MDS for both maximum reported BMI during the lifetime (OR = 2.75, 95% CI 1.12, 6.71) and for BMI at age 50 years (OR=3.23, 95% CI 1.22, 8.52); these estimates were adjusted for age, income, physical activity (walking) and exposure to chemotherapy or benzene. We also observed a significant trend of increased risk with increasing BMI at age 35. Few individuals were obese or overweight at age 18 years. Obesity was associated with increased risk of AML in both males and females in most age groups (Table 3); these models were adjusted for age (continuous) and walking.

As expected, weight at different ages was highly correlated (r=0.64, p<0.0001 for ages 18 and 2 years prior to diagnosis/interview; r=0.69, p<0.0001 for age 18 years to 50 years; r=0.85, p<0.0001 for age 50 to 2 years prior to diagnosis/interview). We were unable to include BMI at different ages in the same logistic regression model because of this multicollinearity; therefore, we were unable to determine whether obesity in early adulthood and obesity two years prior to diagnosis were independent predictors of risk.

We also evaluated weight gain in adulthood as a risk factor for MDS and AML. We did not observe any consistent associations between rate of weight gain in adulthood and risk of either AML or MDS (Table 4). We present data for weight gain between ages 18 – 35 years and 35 years – 2 years ago; however, we also evaluated weight gain from age 18 years – 2 years ago and did not observe any consistent patterns (data not shown). We observed a significant association between weight gain of greater than 1 kg per year between the ages of 18 and 35 years and MDS in females. We also observed a significant association between weight loss > 0.1 kg per year between the ages of 35 years and 2 years prior to diagnosis of MDS, but this association was observed only in women.

Discussion

Our results extend the emerging literature suggesting that obesity is a risk factor for hematologic malignancy [10, 25] and provide evidence that obesity in early life is associated as strongly as obesity in the years immediately prior to diagnosis, although we were not able to determine if these associations were independent given the high correlation of weight at different ages. With a few exceptions, overweight was not a risk factor for either AML or MDS. In fact, we observed the strongest associations in individuals with class II/III obesity (≥ 35 kg/m^2). While we did not observe any consistent associations between weight gain and AML or MDS, it is notable that the majority of the study population gained > 10 kg in adulthood.

Two previous cohort studies and one case control study have reported on overweight and obesity in MDS [11, 12, 26]. The Million Women Study evaluated risk associated with a 10 kg/m^2 increase in BMI so the risk estimates are not directly comparable to ours; however, the results do support a significant increase in risk of MDS in obese women [12]. In the NIH-AARP cohort, Ma et al. reported a relative risk estimate of 2.18 (95% CI 1.51, 3.17) for persons with a BMI ≥ 30 compared with a BMI 18.5–24.9 kg/m^2 [11]. Similar to our study, they found that the association continued to increase when they stratified BMI into six categories, with a relative risk estimate of 2.53 (95% CI 1.45, 4.40) for individuals with a BMI ≥ 35 kg/m^2 [11]. Risk estimates were not stratified by sex, but presumably similar associations were seen for males and females in this study. This is in contrast to our findings, where we observed significant associations between obesity and MDS only among women.

The association between AML and obesity is well-established in the literature, with a meta-analysis and several individual studies reporting a significant increase in risk for AML [10, 12, 27, 31, 33, 34]. Our data suggest that obesity at any time during adulthood increases risk of leukemia. The timing of obesity has not been evaluated extensively; however, one published case-control study of CML reported that obesity at ages 25, 40 and prior to diagnosis were independent risk factors [35]. Overweight has not been consistently associated with AML in the literature, although small but statistically significant associations have been shown in meta-analyses, with risk estimates of 1.09 (1.04, 1.14) [10] and 1.14 (95% CI 1.03, 1.25) [25] for leukemia overall. We found no association with overweight and AML or MDS, although we did not have sufficient power to detect associations as modest as those previously reported.

Previous studies of weight gain in adult solid tumors have shown an increased risk associated with weight gain in adulthood [21, 36–38]. The evidence for an association between weight gain and leukemia is not as well established. One case-control study of CML reported a significant association for weight gain greater than 1 kg/year between the ages of 25 and 40 years and also a higher average weight gain in cases compared with controls [35]. We did not see consistent patterns when we evaluated weight gain during adulthood and AML or MDS. A larger study with more power will be required to further clarify the role of weight gain in adulthood.

The biological mechanism linking obesity to hematologic malignancy has not been established to date. Several potential mechanisms have been proposed [39, 40], including alterations in the metabolism of endogenous hormones such as sex steroids, insulin, insulin-like growth factors, leptin, adiponectin, and fetuin-A [13–18, 41]. Insulin-like growth factor-1 (IGF-1) appears to be particularly relevant as it is known to increase in response to obesity-related insulin resistance [14] and exhibits mitogenic activity in both myeloid and lymphoid leukemia cell lines [13]. Leptin levels, which are also increased in obese individuals [15], have been shown to influence proliferation and differentiation of hematopoietic cells [16] and myeloid leukemia cell lines [15]. It is likely that multiple obesity-related alterations in metabolism are responsible for the association, possibly in the context of changes in the bone marrow microenvironment [42]. The number of adipocytes in the bone marrow increases with age [43] and these cells have been shown to negatively regulate hematopoiesis [44]. While the relationship between bone marrow fat and skeletal fat has not been firmly established [43], data suggest that the amount of adipose tissue in the vertebral bone marrow is correlated with visceral fat [45]. Thus, one might expect a stronger association with body fat distribution compared with obesity in general. Unfortunately, we did not have information on body fat distribution in our study population so we were not able to evaluate this association. A high waist to hip ratio was associated with risk of myeloid leukemia in two previous studies [28, 30], although the findings were significant only in females in one of the studies [30]. Further functional studies may help clarify which of these intriguing biologic mechanisms is driving the association between obesity and hematopoietic malignancy.

There are a number of strengths associated with our study, including rapid case ascertainment for these rapidly fatal diseases and absence of proxy interviews. The rigorous and standardized pathology review is also a strength, as this process ensures that only true cases of AML and MDS were included in the analysis. However, there are also a number of limitations including the potential for recall and survival bias and the reliance on self-report. Self-reported weight is highly correlated with measured weight [46, 47], although there is some evidence that accuracy differs by sex and age [48]. Underestimation of weight or overestimation of height would both cause an underestimate in the calculated BMI. Cases and controls in both studies were frequency matched on age and sex, so any resulting underestimation of BMI is unlikely to differ between cases and controls. Given the poor outcomes associated with both AML and MDS, there is a potential for survival bias. While rapid case ascertainment was used to reduce this possibility, there is a possibility of bias if the cases who died soon after diagnosis differed with respect to their BMI. Selection bias is also possible given the response rates, although we observed no difference between cases and controls with respect to education or income. Further, the prevalence of overweight and obesity at age 65 years in the controls was similar to the prevalence reported for non-Hispanic white males and females ≥ 60 years in the United States in 2011–2012 [19]. Because the majority of our study population was non-Hispanic white, our results may not be generalizable in other populations.

In summary, we found evidence to support a role for obesity in myeloid neoplasms in this analysis of population-based case control studies of AML and MDS in Minnesota. Given the evidence that obesity also increases leukemia mortality [10, 49–51], it is possible that we

could see a rise in incidence and mortality from AML and MDS as the population ages and the prevalence of obesity increases. Since obesity and adulthood weight gain are modifiable risk factors, this suggests that there is an opportunity to reduce the population rates of AML and MDS if the trend of rising obesity rates can be reversed.

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Highlights

- Obesity, but not overweight, is associated with increased risk of AML in both males and females.
- Obesity, but not overweight, is also associated with increased risk of MDS in females.
- Weight change in adulthood was not significantly associated with AML or MDS
- Obesity at multiple time points in adulthood was associated with risk; however, we were unable to determine whether these were independent risk factors given the high correlation of BMI at different ages.
- Our findings extend the growing literature supporting a role of obesity in risk of hematologic malignancy.

Table 1

Selected Characteristics of the Study Population

	Males					Females				
Characteristic	**Controls**	**MDS Cases**	**OR[1] (95% CI)**	**AML Cases**	**OR[1] (95% CI)**	**Controls**	**MDS Cases**	**OR[1] (95% CI)**	**AML Cases**	**OR[1] (95% CI)**
N	773	180		249		615	85		171	
Age (years)										
< 50	102 (13)	5 (3)		55 (22)		120 (20)	2 (2)		69 (40)	
50 – 59	108 (14)	16 (9)		55 (22)		142 (23)	11 (13)		35 (20)	
60 – 69	258 (34)	55 (30)		83 (33)		143 (23)	22 (26)		48 (28)	
70 – 79	239 (31)	67 (37)		56 (23)		173 (28)	31 (36)		19 (11)	
≥ 80	66 (9)	37 (21)		0		37 (6)	19 (22)		0	
Race										
White	759 (98)	176 (98)		238 (96)		591 (99)	84 (99)		163 (95)	
Other	14 (1.8)	4 (2)		11 (4)		24 (1.1)	1 (1.1)		8 (5)	
Education										
≤ HS grad	236 (31)	60 (34)	*Ref*	73 (30)	*Ref*	197 (32)	37 (44)	*Ref*	49 (29)	*Ref*
Some post HS	253 (33)	50 (28)	1.00 (0.65, 1.54)	95 (39)	1.10 (0.77, 1.58)	207 (34)	19 (23)	0.62 (0.34, 1.13)	66 (39)	1.03 (0.67, 1.60)
College grad	282 (37)	69 (38)	1.12 (0.75, 1.66)	78 (32)	0.84 (0.58, 1.21)	207 (34)	28 (33)	1.13 (0.65, 1.98)	56 (33)	0.77 (0.49, 1.22)
P Trend			0.83		0.30			0.15		0.35
Household Income										
≤ $40,000	233 (31)	69 (40)	*Ref*	75 (31)	*Ref*	263 (44)	43 (52)	*Ref*	74 (44)	*Ref*
$40,000– $80,000	307 (41)	62 (35)	0.78 (0.53, 1.16)	108 (45)	1.06 (0.75, 1.50)	219 (37)	30 (37)	1.28 (0.75, 2.18)	57 (34)	0.81 (0.54, 1.21)
> $80,000	219 (29)	45 (25)	0.94 (0.61, 1.46)	59 (24)	0.78 (0.53, 1.16)	117 (20)	9 (11)	0.83 (0.38, 1.84)	36 (22)	0.93 (0.59, 1.49)
P Trend			0.44		0.25			0.49		0.60
Smoking Status[2]										
Never smoker	342 (45)	68 (38)	*Ref*	94 (39)	*Ref*	352 (58)	42 (49)	*Ref*	85 (50)	*Ref*
Former smoker	335 (44)	100 (56)	1.30 (0.91, 1.84)	105 (43)	1.38 (0.99, 1.92)	186 (30)	37 (44)	**1.67 (1.02, 2.72)**	56 (33)	1.40 (0.94, 2.08)
Current smoker	90 (12)	11 (6)	0.84 (0.42, 1.68)	45 (18)	**1.58 (1.03, 2.44)**	72 (12)	6 (7)	0.89 (0.36, 2.22)	29 (17)	1.46 (0.88, 2.43)
P Trend			0.22		**0.05**			0.09		0.15
Personal History of cancer										
No	665 (86)	131 (73)	*Ref*	213 (86)	*Ref*	550 (89)	56 (66)	*Ref*	140 (82)	*Ref*

	Males					Females				
Characteristic	**Controls**	**MDS Cases**	**OR[1] (95% CI)**	**AML Cases**	**OR[1] (95% CI)**	**Controls**	**MDS Cases**	**OR[1] (95% CI)**	**AML Cases**	**OR[1] (95% CI)**
Yes	108 (14)	49 (27)	**1.68 (1.12, 2.50)**	36 (14)	1.41 (0.92, 2.16)	65 (11)	29 (34)	**3.18 (1.86, 5.42)**	31 (18)	**3.01 (1.82, 4.98)**

OR: Odds Ratio; CI: Confidence Interval

Numbers may not sum to total due to missing values

Odds ratios not computed for age (matching variable), race and ethnicity.

[1]ORs adjusted for age as a continuous variable

[2]Smoking status includes cigarette smoking only

Table 2

Association between obesity throughout adulthood and MDS in males and females

	Males					*Females*				
Characteristic	**Cases**	**Controls**	**OR[1]**	**95% CI**	***p*-value**	**Cases**	**Controls**	**OR[1]**	**95% CI**	***p*-value**
N	180	773				85	615			
BMI at age 18										
< 18.5	13 (7)	41 (6)	1.19	0.57–2.52	0.64	5 (6)	96 (16)	**0.26**	**0.10–0.70**	**0.008**
18.5–21.9	51 (29)	252 (34)	*Ref*			55 (68)	286 (48)	*Ref*		
22.0–24.9	62 (35)	289 (39)	0.95	0.62–1.46	0.82	15 (19)	133 (23)	0.67	0.35–1.30	0.23
25.0 – 29.9	41 (23)	142 (19)	1.37	0.84–2.23	0.20	4 (5)	60 (10)	0.50	0.16–1.57	0.24
≥ 30.0	8 (5)	26 (4)	2.32	0.93–5.81	0.07	2 (3)	16 (3)	1.02	0.18–5.73	0.98
5 kg/m^2 increment			1.23	0.94–1.61	0.14			1.16	0.80–1.69	0.43
BMI at age 35[2]										
18.5 – 24.9	62 (36)	302 (42)	*Ref*			46 (58)	375 (69)			
25.0 – 29.9	80 (47)	312 (44)	1.11	0.74–1.61	0.66	23 (29.1)	114 (21)	**2.02**	**1.10–3.70**	**0.02**
≥ 30.0	28 (16)	101 (14)	1.53	0.90–2.61	0.12	10 (13)	54 (10)	**3.18**	**1.34–7.51**	**0.009**
5 kg/m^2 increment			1.18	0.94–1.48	0.15			**1.47**	**1.13–1.91**	**0.004**
BMI at age 50[2]										
18.5 – 24.9	43 (25)	170 (26)	*Ref*			34 (44)	224 (48)			
25.0 – 29.9	84 (50)	323 (50)	0.97	0.63–1.49	0.88	25 (32)	147 (31)	1.17	0.64–2.12	0.62
30.0 – 34.9	31 (18)	119 (18)	1.11	0.64–1.91	0.71	10 (123)	68 (14)	1.52	0.67–3.43	0.32
≥ 35.0	11 (7)	41 (6)	1.24	0.55–2.75	0.61	9 (12)	32 (7)	**3.23**	**1.22–8.52**	**0.02**
5 kg/m^2 increment			1.09	0.90–1.33	0.37			**1.27**	**1.01–1.59**	**0.04**
BMI, 2 years ago[2]										
18.5 – 24.9	35 (21)	160 (21)	*Ref*			24 (30)	212 (36)	*Ref*		
25.0 – 29.9	72 (41)	330 (44)	0.90	0.56–1.45	0.77	25 (31)	183 (31)	0.97	0.51–1.85	0.93
30.0 – 34.9	49 (28)	176 (23)	1.20	0.72–2.01	0.41	17 (21)	112 (19)	1.16	0.57–2.40	0.68
≥ 35.0	18 (10)	85 (11)	0.97	0.50–1.88	0.99	14 (18)	77 (13)	1.60	0.73–3.54	0.24
5 kg/m^2 increment			1.09	0.92–1.29	0.34			1.12	0.93–1.35	0.25
BMI, max [a]										
18.5 – 24.9	12 (7)	67 (9)	*Ref*			9 (11)	130 (22)	*Ref*		

			Males					*Females*		
Characteristic	**Cases**	**Controls**	**OR[1]**	**95% CI**	***p*-value**	**Cases**	**Controls**	**OR[1]**	**95% CI**	***p*-value**
25.0 – 29.9	67 (38)	312 (42)	0.93	0.46–1.89	0.85	25 (31)	194 (33)	1.72	0.73–4.02	0.21
30.0 – 34.9	63 (36)	227 (30)	1.12	0.55–2.27	0.76	24 (30)	142 (24)	2.18	0.91–5.21	0.08
≥ 35.0	33 (19)	144 (19)	1.10	0.52–2.35	0.80	22 (28)	127 (21)	**2.75**	**1.12–6.71**	**0.03**
5 kg/m^2 increment			1.07	0.91–1.25	0.41			**1.24**	**1.04–1.47**	**0.02**

OR: Odds Ratio; CI: Confidence Interval

Numbers may not sum to total due to missing values

[1]ORs adjusted for age as a continuous variable, household income (≤ $40,000, $40,000 – $80,000, ≥ $80,000), walking (< 4x/month, 1–3x/week, ≥ 4x/week), exposure to chemotherapy, exposure to benzene

[2]BMI < 18.5 excluded from analysis

Table 3

Association between obesity throughout adulthood and AML in males and females

	Males					*Females*				
Characteristic	**Cases**	**Controls**	**OR[1]**	**95% CI**	***p*-value**	**Cases**	**Controls**	**OR[1]**	**95% CI**	***p*-value**
N	249	773				171	615			
BMI at age 18										
< 18.5	11 (5)	43 (6)	1.08	0.52–2.24	0.83	23 (14)	101 (17)	0.92	0.54–1.58	0.77
18.5 – 21.9	63 (26)	258 (34)	*Ref*			70 (42)	294 (48)	*Ref*		
22.0 – 24.9	84 (35)	295 (38)	1.16	0.80–1.69	0.43	44 (27)	137 (23)	1.24	0.80–1.94	0.33
25.0 – 29.9	69 (28)	145 (19)	**1.73**	**1.15–2.60**	**0.008**	19 (11)	60 (10)	0.97	0.53–1.79	0.93
≥ 30.0	16 (7)	23 (3)	1.96	0.97–3.97	0.06	12 (7)	16 (3)	**2.55**	**1.13–5.77**	**0.03**
5 kg/m^2 increment			**1.31**	**1.07–1.60**	**0.009**			**1.26**	**1.02–1.55**	**0.03**
BMI at age 35[2]										
18.5 – 24.9	79 (35)	310 (42)	*Ref*			87 (61)	389 (70)	*Ref*		
25.0 – 29.9	101 (45)	319 (44)	1.21	0.86–1.70	0.27	34 (24)	117 (21)	1.20	0.76–1.92	0.44
30.0 – 34.9	33 (15)	83 (11)	1.31	0.80–2.13	0.28	11 (8)	33 (6)	1.24	0.58–2.63	0.58
≥ 35.0	11 (5)	20 (3)	1.68	0.75–3.74	0.21	10 (7)	21 (4)	1.53	0.66–3.54	0.32
5 kg/m^2 increment			**1.21**	**1.01–1.45**	**0.04**			1.10	0.92–1.32	0.29
BMI at age 50[2]										
18.5 – 24.9	38 (20)	173 (26)	*Ref*			44 (44)	233 (48)	*Ref*		
25.0 – 29.9	89 (47)	334 (50)	1.26	0.82–1.93	0.30	27 (27)	152 (31)	0.95	0.56–1.62	0.85
30.0 – 34.9	48 (25)	121 (18)	**1.73**	**1.05–2.84**	**0.03**	14 (14)	68 (14)	1.04	0.53–2.07	0.91
≥ 35.0	14 (7)	42 (6)	1.22	0.59–2.49	0.60	14 (14)	33 (7)	**2.20**	**1.04–4.68**	**0.04**
5 kg/m^2 increment			1.16	0.97–1.38	0.10			**1.20**	**1.01–1.43**	**0.04**
BMI, 2 years ago[2]										
18.5 – 24.9	34 (14)	161 (21)	*Ref*			58 (35)	221 (37)	*Ref*		
25.0 – 29.9	99 (40)	342 (44)	1.53	0.98–2.39	0.06	47 (28)	188 (31)	1.08	0.69–1.69	0.74
30.0 – 34.9	75 (31)	181 (24)	**2.24**	**1.40–3.59**	**0.001**	32 (19)	113 (19)	1.45	0.87–2.42	0.16
≥ 35.0	37 (15)	85 (11)	**2.22**	**1.28–3.85**	**0.005**	31 (18)	79 (13)	**1.85**	**1.08–3.15**	**0.02**
5 kg/m^2 increment			**1.26**	**1.10–1.44**	**0.001**			**1.18**	**1.05–1.32**	**0.001**

	Males					*Females*				
Characteristic	**Cases**	**Controls**	**OR*1***	**95% CI**	***p*-value**	**Cases**	**Controls**	**OR*1***	**95% CI**	***p*-value**
BMI, max[2]										
18.5 – 24.9	15 (6)	68 (9)	*Ref*			34 (20)	134 (22)	*Ref*		
25.0 – 29.9	78 (32)	321 (42)	1.17	0.63–2.19	0.62	48 (28)	203 (33)	1.07	0.64–1.78	0.79
30.0 – 34.9	95 (39)	234 (30)	**2.11**	**1.13–3.93**	**0.02**	38 (22)	143 (23)	1.30	0.75–2.24	0.35
≥ 35.0	56 (23)	145 (19)	1.81	0.94–3.48	0.08	50 (29)	129 (21)	**1.98**	**1.17–3.36**	**0.01**
5 kg/m^2 increment			**1.23**	**1.09–1.38**	**0.001**			**1.22**	**1.09–1.37**	**0.001**

OR: Odds Ratio; CI: Confidence Interval

*Numbers may not sum to total due to missing values

*1*ORs adjusted for age as a continuous variable and walking (< 4x/month, 1–3x/week, ≥ 4x/week)

*2*BMI < 18.5 excluded from analysis

Table 4

Weight change in adulthood and risk of MDS and AML in males and females

	Males					Females				
	Cases	**Controls**	**OR**	**95% CI**	**p-value**	**Cases**	**Controls**	**OR**	**95% CI**	**p-value**
MDS[1]										
Δ Kg Age 18 – 35										
Loss (> 0.1 kg/y)	9 (5)	22 (3)	1.75	0.65–4.71	0.27	5 (6)	44 (8)	1.17	0.36–3.86	0.79
No change (0 ± 0.1 kg/y)	21 (12)	74 (10)	*Ref*			14 (18)	90 (16)	*Ref*		
Gain (0.1–0.5 kg/y)	77 (44)	270 (38)	1.24	0.69–2.25	0.47	30 (38)	232 (42)	1.04	0.50–2.20	0.91
Gain (0.5–1.0 kg/y)	48 (27)	238 (33)	0.97	0.52–1.80	0.92	19 (24)	134 (24)	1.45	0.64–3.29	0.38
Gain (> 1 kg/y)	21 (12)	110 (15)	1.00	0.49–2.06	0.99	12 (15)	53 (10)	**4.03**	**1.49–10.91**	**0.006**
p-trend					0.59					**0.03**
Δ Kg Age 35 - diagnosis										
Loss (> 0.1 kg/y)	22 (13)	79 (11)	1.58	0.80–3.12	0.19	13 (16)	49 (9)	**2.75**	**1.00–7.52**	**0.05**
No change (0 ± 0.1 kg/y)	28 (16)	131 (18)	*Ref*			12 (15)	90 (16)	*Ref*		
Gain (0.1–0.5 kg/y)	82 (47)	288 (40)	1.39	0.84–2.29	0.20	29 (36)	206 (38)	1.00	0.46–2.16	0.99
Gain (0.5–1.0 kg/y)	32 (18)	142 (20)	1.43	0.78–2.62	0.25	19 (24)	112 (21)	1.38	0.59–3.23	0.46
Gain (> 1 kg/y)	12 (7)	75 (10)	1.36	0.61–3.05	0.45	7 (9)	89 (16)	1.47	0.49–4.45	0.49
p-trend					0.69					0.23
AML[2]										
Δ Kg Age 18 – 35										
Loss (> 0.1 kg/y)	12 (5)	22 (3)	1.48	0.60–3.64	0.39	13 (9)	46 (8)	1.12	0.47–2.68	0.80
No change (0 ± 0.1 kg/y)	21 (9)	76 (10)	*Ref*			16 (11)	90 (16)	*Ref*		
Gain (0.1–0.5 kg/y)	70 (31)	275 (38)	0.94	0.53–1.65	0.82	69 (49)	240 (42)	1.80	0.96–3.36	0.07
Gain (0.5–1.0 kg/y)	71 (32)	245 (34)	0.97	0.55–1.71	0.91	31 (22)	138 (24)	1.19	0.59–2.38	0.63
Gain (> 1 kg/y)	49 (22)	113 (15)	1.37	0.75–2.53	0.31	13 (9)	54 (10)	0.83	0.35–1.98	0.68
p-trend					0.40					0.12
Δ Kg Age 35 - diagnosis										
Loss (> 0.1 kg/y)	21 (9)	80 (11)	0.77	0.41–1.45	0.42	19 (14)	50 (9)	1.24	0.57–2.67	0.59
No change (0 ± 0.1 kg/y)	37 (16)	134 (18)	*Ref*			21 (15)	93 (17)	Ref		
Gain (0.1–0.5 kg/y)	81 (36)	299 (41)	1.09	0.69–1.72	0.71	36 (26)	212 (38)	0.82	0.45–1.51	0.53

	Males					Females				
	Cases	**Controls**	**OR**	**95% CI**	**p-value**	**Cases**	**Controls**	**OR**	**95% CI**	**p-value**
Gain (0.5–1.0 kg/y)	47 (21)	144 (20)	1.12	0.68–1.86	0.66	26 (19)	116 (21)	1.08	0.56–2.07	0.83
Gain (> 1 kg/y)	39 (17)	75 (10)	1.30	0.74–2.29	0.37	38 (27)	91 (16)	1.44	0.75–2.76	0.28
					0.60					0.45

OR: Odds Ratio; CI: Confidence Interval

Numbers may not sum to total due to missing values

[1]ORs adjusted for age (continuous), household income (≤ $40,000, $40,000 – $80,000, ≥ $80,000) walking (< 4x/month, 1–3x/week, ≥ 4x/week), exposure to chemotherapy, exposure to benzene

[2]ORs adjusted for age as a continuous variable and walking (< 4x/month, 1–3x/week, ≥ 4x/week)