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Metabolic factors and blood cancers among 578.000 adults in the Metabolic Syndrome and Cancer Project (Me-Can)

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Summary

Background: We investigated associations between metabolic factors and blood cancer subtypes.

Methods: Data on body mass index (BMI), blood pressure, blood glucose, total cholesterol and triglycerides from seven prospective cohorts were pooled (N=578,700; mean age=44 years).

Relative risks of blood cancers were calculated from Cox regression models.

Results: During mean follow-up of 12 years, 2,751 incident and 1,070 fatal cases of blood cancers occurred. Overall, higher BMI was associated with an increased blood cancer risk. In gender specific subgroup analyses, BMI was positively associated with blood cancer risk ($p = 0.002$), lymphoid neoplasms ($p = 0.01$), and Hodgkin lymphoma ($p = 0.02$) in women. Further associations with BMI were found for high grade B-cell lymphoma ($p = 0.02$) and chronic lymphatic leukemia in men ($p = 0.05$) and women ($p = 0.01$). Higher cholesterol levels were inversely associated with myeloid neoplasms in women ($p = 0.01$), particularly acute myeloid leukemia ($p = 0.003$) and glucose was positively associated with chronic myeloid leukemia in women ($p = 0.03$). In men, glucose was positively associated with risk of high grade B-cell lymphoma and multiple myeloma, while cholesterol was inversely associated with low grade B-cell lymphoma. The metabolic syndrome (MetS) score was related to 48% increased risk of Hodgkin lymphoma among women.

Conclusions: BMI showed up as the most consistent risk factors, particularly in women. For none of other metabolic factors a clear pattern was found.

Introduction

The incidence of malignancies of the hematopoietic and lymphatic tissue has increased during the past decades, but recent reports indicate that the incidence rates are leveling off. The incidence is higher in men than in women¹. Blood cancers are a heterogeneous disease group and the current classification was introduced by the World Health Organization (WHO) in order to increase comparability^{2,3}. There is evidence that immunosuppression and infections as well as ultraviolet radiation, chemical exposures, and genetic susceptibility are involved in the pathogenesis of blood cancers. Except for these factors, the etiology of blood cancers is largely unknown^{4,5}.

The metabolic syndrome (MetS) is characterized by obesity, hyperglycemia, dyslipidemia and high blood pressure which are established risk factors in cardiovascular disease⁶. Components of the MetS have been reported to be associated with an increased risk of cancer incidence and mortality^{7,8}. Several cohort studies have shown statistically significant positive associations between body mass index (BMI) and increased risk of lymphoma, in particular, in high grade B-cell lymphoma^{9,10}, myeloid leukemia¹¹, and multiple myeloma⁵ whereas others have found no associations between BMI and the overall risk of non-Hodgkin lymphoma (NHL)¹² or its subtypes¹³. In addition, other metabolic factors such as blood glucose¹⁴ and lipids^{15,16} have been linked to an increased risk of blood cancers. Diabetes has been associated with a moderate increased risk of NHL¹⁷ and of B-cell NHL in men¹⁴. High HDL-cholesterol and triglyceride concentration have been related to a reduced risk of NHL^{15,16}. On the whole, contradictory information exists regarding the role of different metabolic markers in relation to blood cancer risk^{4,5}.

The aim of our study was to examine the associations of individual and combined metabolic factors with blood cancer incidence and mortality including subtypes and selected entities in the large prospective Me-Can project.

Material and methods

Study population

A comprehensive description of the Metabolic Syndrome and Cancer (Me-Can) project has previously been published¹⁸. In brief, seven cohorts were pooled: the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP; baseline examination 1988-2002) from Austria, the Oslo study I cohort (Oslo; 1972-73), the Norwegian Counties study (NCS; 1974-83), the Cohort of Norway (CONOR; 1995-2003) and the Age 40 Programme (40-y; 1994-99) from Norway and the Västerbotten Intervention Project (VIP; 1985-2005) and the Malmö Preventive Project (MPP; 1974-92) from Sweden. The Me-Can study has been approved by research ethics committees in their respective countries.

All participants had undergone at least one health examination. Participants' height and weight were measured similarly in all centers; in light indoor clothes and no shoes. Blood pressure was measured under different conditions with regard to resting time, body positions and equipment¹⁸. Blood concentrations of glucose, total cholesterol and triglycerides were measured in a fasting or non-fasting state, by enzymatic or non-enzymatic methods. Data on smoking status were also available in all cohorts.

The inclusion criteria for the Me-Can study have been previously described in detail¹⁸. In brief, after exclusion of subjects with unrealistic or missing baseline data or prevalent cancer diagnosis, the Me-Can cohort consists of 578,700 subjects. To reduce the possibility of reverse causation, follow-up started one year after the baseline examination, which resulted in further exclusion of 3,314 subjects. Thus, 575,386 subjects' data were included in the analyses.

Exposure variables

BMI (weight (kg) /height² (m)), mean blood pressure ((systolic blood pressure + diastolic blood pressure)/ 2), glucose, cholesterol and triglycerides were standardized to Z-score variables with

mean = 0 and SD = 1 to adjust for different measurement methods in the cohorts and thus to increase comparability of risk estimates between metabolic factors. A score for the MetS was calculated by adding the individual Z-scores and the sum was also standardized. The variables were standardized separately for the seven sub-cohorts, sex, and glucose; cholesterol, triglycerides and the combined score were additionally standardized for fasting time (<4 hours, 4-8 hours, >8 hours). In order to approximate normal distribution, glucose and triglycerides were log-transformed before standardization. Quintile cut-points were determined for the exposure variables within sub-cohorts and sex; and for glucose, cholesterol and triglycerides also in categories of fasting time. In order to make the variables comparable on a continuous scale and to create a combined MetS variable, a score for the metabolic syndrome was constructed by adding the individual z-scores and standardized separately for the six sub-cohorts and for fasting time. Relative risks were calculated for the increment of 1 z-score. In addition, we estimated risks in groups according to cut-offs as defined by WHO for obesity (BMI < 25, 15-29.9, >30 kg/m²) and hypertension (systolic blood pressure <120, 120-139.9, >140 mmHg, diastolic blood pressure >80, 80-89.9, 90 mmHg).

Endpoints

Incident cases of cancers were identified through linkages with the national cancer registries. Lymphoma and leukemia cases were identified according to the International Classification of Diseases, seventh revision (ICD-7). Based on International Classification of Diseases in oncology (ICD-O-2) codes and the Systematized Nomenclature of Medicine (SNOMED) (Norway, Sweden) and ICD-O-3 codes (Austria), all cancers were subsequently recoded according to the WHO classification². Cases with equivocal codes were transformed to an unspecified category (N=181). Data on mortality were obtained from national mortality registries. The causes of death were classified according to cancer sites as grouped in the Eurostat European shortlist for causes of death¹⁹.

Based on the original cell-line we categorized the subtypes as myeloid and lymphoid neoplasms. We focused on the following subtypes of blood cancer: acute myeloid leukemia (AML), myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), high and low grade B-cell lymphoma (high and low B-cell NHL), T-cell non-Hodgkin lymphoma (T-cell NHL), Hodgkin lymphoma (HL) and multiple myeloma (MM). Results for selected common blood cancer entities are presented in a supplemental table: chronic myeloid leukemia (CML), diffuse large B-cell NHL (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia (CLL)¹.

Person-years for participants were counted until the end date of the follow-up, cancer diagnosis, emigration, or death. Participants were censored in analyses of cancer incidence as followed: December 31, 2003 (Austria), 2005 (Norway) and 2006 (Sweden) and in analyses of cancer mortality December 31, 2003, 2004 and 2005, respectively.

Statistical analysis

Cox regression models with age as the time variable were fitted to obtain hazard ratios denoted as relative risk (RR) with 95% confidence intervals (CIs) of blood cancer incidence and mortality in order to control for age, because the cancer incidence is closely related to age. We performed the analyses separately for men and women, because there was evidence for sex-differential associations¹⁰. All analyses were performed adjusted for age at baseline (years, continuous), and smoking status (never, current and former smokers, and unknown) since for some entities associations have been observed²⁰. The models were stratified by sub-cohorts and year of birth (in categories ≤ 1929 , 1930 -39, 1940-49, 1950-59 and ≥ 1960) in order to account for differences in the study centers and time effects, respectively. We investigated the association between metabolic factors and blood cancer risk by exposures in quintiles. And additionally we examined the data using continuous Z-score variables, in order to appraise a combined variable for the metabolic factors and to increase statistical power. Test for trend across quintiles was calculated using the median levels of the exposure variable. Two-sided p-values of 0.05 were

considered statistically significant. All calculations were carried out with the statistical software package SAS release 9.2 (SAS Institute, Cary, N.C.; USA) and R (version 2.7.2) for calculation of random error.

Correction of the measurement error

The combined effect of measurement errors of the different exposures (BMI, mid blood pressure, glucose, cholesterol and triglycerides) and long-term fluctuations within the individuals may lead to regression dilution bias. In order to account for the measurement error of different exposures and variation of exposures during follow-up, corrections were made by calculating regression dilution ratio (RDR)²¹. In brief, we used data from 133,820 subjects with repeated health examinations comprising 406,364 observations in the Me-Can cohort in order to calculate the RDR using the Rosner regression model as suggested by Wood et al.²¹. Mean time since the baseline measurement was 6.9 (SD 3.9) years. Corrections of the RRs for RDR were obtained by $[\exp(\log(RR)/RDR)]$. The sex-specific RDR used in the analysis were in men and women respectively: BMI (0.90, 0.90), mid blood pressure (0.53, 0.56), ln blood glucose (0.28, 0.27), cholesterol (0.64, 0.66), ln triglycerides (0.51, 0.50) and MetS score (0.68, 0.69).

The regression calibration model (RC) was applied to models including all metabolic factors simultaneously for Z-score analysis, because RDR was not suitable in models using more than one variable measured with error. In the Cox regression models the exposure of interest as measured was replaced by a predicted value.

Results

Mean age at baseline was 43.8 (SD 11.1) years in men and 44.0 (SD 12.3) years in women. Men were on average followed for 13.3 (SD 9.3) years and women for 11.1 (SD 7.0) years (table 1). Among participants with a follow-up of at least one year 2,751 incident blood cancers (1,710 in men and 1,041 in women) were identified. A total of 1,070 individuals died due to blood cancer and 41,604 subjects died due to other causes. Mean age at diagnosis of blood cancer was 62.5

(SD 11.2) years in men and 62.4 (SD 11.9) years in women. The most common diagnoses of incident cases were low grade B-cell NHL, MM, CML, and AML.

Metabolic factors and blood cancers incidence and mortality, myeloid and lymphoid neoplasms

There was a significant association between higher BMI and increased blood cancer risk in the entire group (table 2). Gender specific subgroup analyses of BMI per unit increase of Z-score showed among women an association with increased blood cancer incidence (1.12, 1.05-1.19, table 2) and increased risk of lymphoid neoplasms (1.15; 1.05-1.25). For both relationships statistically significant linear associations were found (p for trend 0.002 and 0.010, respectively). Cholesterol by Z-score was inversely related to risk of blood cancers among women (0.88; 0.80-0.97).

Blood pressure by quintiles was positively associated with blood cancer mortality in men (p for trend 0.008, table 2) and by Z-score in men (1.19; 1.03-1.36). Increased relative risks were also observed for categories according to WHO definitions for hypertension (Figure 1a).

Subgroup analyses in myeloid neoplasms (AML, MPN, MDS and CML)

A lower relative risk of myeloid neoplasms was identified in women with highest cholesterol levels (comparing the first quintile and the fifth quintile) in women (p for trend 0.014, table 3). The same was identified for AML among women and for MPN among both men and women. In contrary, an increased risk of CML was observed with increasing glucose levels in women (p for trend 0.033) and increasing triglycerides levels among men (p for trend 0.037, supplemental table).

Subgroup analysis in lymphoid neoplasms (B-cell NHL (high, low), T-cell NHL, HL, MM, and DLBCL, FL and CLL)

1 In subset analyses of specific lymphoid malignancies, a positive association between BMI and
2 risk of high grade B-cell NHL among men was identified (p for trend 0.023). Among women,
3 increased relative risks for lymphoid neoplasm (Figure 1b) were also observed for adiposity
4 based on WHO definitions (Figure 1b).

5 In women the risk of HL was also associated with a higher BMI (p for trend 0.015), whereas in
6 contrary a reduced risk of T-cell lymphoma was found (p for trend 0.009).

7 In men, higher glucose levels categorized in quintiles showed increased risks of high grade B-
8 cell NHL and MM (p for trend 0.020 and 0.019, respectively). Cholesterol (p for trend 0.023)
9 and triglycerides (p for trend 0.027) were inversely associated with low grade B-cell NHL.
10 Consistent results were present in models including Z-scores of metabolic factors. MetS score
11 per increase of 1 SD was associated with reduced risk of T-cell NHL among men (RR, 0.55;
12 0.34-0.91; table 4) and increased risk of HL among women (1.48; 1.05-2.09).

13 Concerning common blood cancer entities (please see supplemental table) increasing BMI was
14 related to increased risk of CLL in men and women (p for trend 0.050 and 0.011, respectively).
15 Among women, reduced risk of DLBCL was observed for increasing triglycerides (p for trend
16 0.025) and increased risk of FL was found for increasing cholesterol and triglycerides (p for
17 trend 0.027 and 0.017, respectively).

18 19 **Discussion**

20 The aim of this study was to analyse associations of metabolic factors with incident and fatal
21 blood cancer. In addition, subgroup analyses were performed including common entities and
22 mortality in order to generate hypothesis²².

23 In the entire group as well as in gender specific subgroup analyses of single factors, BMI was the
24 most consistent risk factor for blood cancer risk overall and lymphoid neoplasms in women but
25 not in men. Cholesterol concentration was inversely related to myeloid neoplasms particularly to
26 AML among women.

1 The major strengths of our analyses are the prospective design of a large pooled cohort
2 including more than 2,500 cases of incident blood cancer, and the corrections for measurement
3 errors of the components of the metabolic syndrome which was possible due to the large number
4 of repeated measurements. Mean follow-up of the cohort was 12 years. Our large sample size
5 enabled us also to investigate the association of metabolic factors with subtypes of blood cancer.
6 In addition, identification of disease outcome was performed by record linkage with high quality
7 cancer registries¹⁸ with a high coverage.

8
9 Potential limitations of the study are the differences in measurements of exposures across the
10 included Me-Can centers. In order to account for center characteristics the analyses were
11 performed stratified by cohort. The lack of information on medication, physical activity, alcohol
12 consumption, is clear shortcomings of the analysis. Multiple comparisons without corrections
13 were performed which should be considered for interpretation of the results. However, consistent
14 results were found for Z-score in and quintile analyses within multivariate models. Inclusion of
15 all metabolic factors simultaneously in the models on Z-scores did not substantially change the
16 strength of most associations (data not shown), indicating an independent relationship between
17 the metabolic factors. Different definitions of the MetS exist²³. However, all existing definitions
18 consider indicators of obesity, insulin resistance, dyslipidemia, and blood pressure suggesting
19 that differences in definitions are unlikely to affect our observations.

20
21 In contrast to a meta-analysis of cohort studies²⁴, we found no association between BMI and
22 AML. Our findings of an inverse association between cholesterol and myeloid neoplasms in
23 particular AML is consistent with results from experimental studies^{25, 26}. Reverse causation is
24 thought to contribute to the inverse association²⁷ since time-dependent associations have been
25 reported between cholesterol and cancer risk²⁸. Results from experimental studies suggest that
26 cholesterol may regulate VEGF:VEGFR-1 signaling on subsets of acute leukemia modulating
27 cell migration and influence disease progression²⁹. We found positive associations between

glucose and CML risk in women while other authors found an association between diabetes and CML in men¹⁴.

Our findings of a positive association of BMI with lymphoid neoplasms are in line with previous reports^{30,31}. Our observation of increased risk of high grade B-cell NHL among obese individuals is consistent with recent reports from cohort studies^{10,30} and pooled analysis^{9,24}. Experimental studies have shown that leptin induced the proliferation and differentiation of hematopoietic cells³² and modulates the immune function in the hematopoietic process particularly in the B-cell compartment³³. Different pathways including glucose metabolism, levels of free fatty acids, inflammatory factors and adipokines have been suggested to link the MetS with cancer risk³⁴. Other possible mechanisms include estrogen as adipose tissue is part of estrogen synthesis^{8,7}.

We cannot rule out reverse causality in the inverse associations between MetS score and T-cell NHL. However, in lag-time analyses leaving out the first 5 years of follow-up resulted in a statistically significant relative risk estimates for T-cell NHL. Longer follow-up of the cohorts may facilitate analyses with longer lag times. Our finding that MetS score was associated with increased risk of HL among women is in line with data showing a correlation of HL and obesity^{35,36}.

In line with previous research¹⁰ we observed increased risk of MM among overweight men. Experimental data suggested that adipose tissue may be linked by leptin and adiponectin to MM³⁷. Our findings of no clear relationships of BMI with DLBCL and FL fits in the picture of heterogeneous results^{8,10,38,31}. Previous research indicated that associations with NHL may depend on the age of overweight and obese subjects^{38,39}. In our study, increased BMI was associated with increased risk of CLL in men and women, while other authors found no association¹⁰. A recent case-control study found an association between obesity and t(14;18)-

positive DLBCL but not t(14;18)-negative DLBCL suggesting that subtype-specific association may exist⁴⁰.

Consistent with previous data on hypertension and blood cancer incidence, we found no association between these entities^{41,42}. In contrast, Tulinius et al. observed increased risk of lymphoma among hypertensive men in a prospective study among Icelanders¹².

Data from our study provided no evidence for a relationship between glucose concentration and blood cancer risk, except for MM and high B-cell NHL in men. Data on blood glucose levels or diabetes mellitus and blood cancer have been inconsistent, increased risk^{41,43} as well as no association^{14,44} has been reported. Meta-analyses among patients with preexisting diabetes mellitus revealed that diabetes was associated with increased NHL incidence¹⁷. Results from *in-vitro* studies suggested that insulin is involved in the malignant transformation of myeloma cells^{45,46}.

In conclusion, we found in the entire cohort as well as in subgroup analyses that BMI was positively related to blood cancer risk and, in particular, to lymphoid neoplasms risk in women; cholesterol was inversely related to myeloid neoplasms. Our study supports the hypothesis of a gender-specific correlation between metabolic factors and blood cancer subtypes which needs to be elucidated further.

Conflict of interest

None declared

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1 Table 1: Description of the study population

		Men	Women
Cohort N (%)			
Norway	Oslo	16, 690 (6)	-
	NCS	25,848 (9)	24,993 (9)
	CONOR	51,666 (18)	57,300 (20)
	40-y	60, 534 (21)	67,989 (24)
Austria	VHM&PP	72,569 (25)	86, 153 (30)
Sweden	VIP	38,633 (13)	40,437 (14)
	MPP	22, 128 (8)	10,446 (4)
Total		288,068	287,318
Follow-up (years)			
Mean (SD)		13.3 (9.3)	11.1 (7.0)
Categories N (%)	0-9	150, 831 (53)	161,469 (56)
	10-19	84, 562 (29)	97,131 (34)
	20+	52,675 (18)	28,718 (10)
Baseline age (years)			
Mean (SD)		43.8 (11.1)	44.0 (12.3)
Categories N (%)	-29	24,291 (8)	30,045 (10)
	30-39	47,715 (17)	44,038 (15)
	40-49	147,947 (51)	134,053 (47)
	50-59	33,291 (12)	39,677 (14)
	60-69	26,031 (9)	27,048 (10)
	70+	8,793 (3)	12,457 (4)
Year of birth N (%)			
Categories N (%)	-1929	37,564 (13)	28,275 (10)
	1930-39	50,225 (17)	44,114 (15)
	1940-49	46,941 (16)	42,246 (15)
	1950-59	104,869 (36)	116,570 (41)
	1960-	48,469 (17)	56,113 (19)
Fasting time (hours) N (%)			
Categories N (%)	<4	119,875 (41)	121,766 (42)
	4-8	30,579 (11)	26,661 (9)
	> 8	137,614 (48)	138,891 (49)
Smoking status N (%)			
	Never-smoker	112,815 (39)	143, 948 (50)
	Ex-smoker	85,624 (30)	72,302 (25)
	Smoker	88,772 (31)	70, 378 (25)
	Unknown	857 (0)	690 (0)
BMI (kg/m ²)			
Mean (SD)		25.7 (3.5)	24.9 (4.4)
Categories N (%)	< 25.0	130, 416 (45)	169,755 (59)
	25.0-29.9	127, 014 (44)	82,387 (29)
	30+	30, 638 (11)	35,176 (12)

Mid BP, mean (SD)		106.9 (12,7)	101.8 (14.2)
Glucose mmol/l, median (IQR)		5.2 (4.7;5.7)	5.0 (4.6; 5.5)
Cholesterol mmol/l, mean (SD)		5.7 (1.2)	5.6 (1.2)
Triglycerides mmol/l, median (IQR)		1.5 (1.1;2.3)	1.1 (0.8; 1.6)

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Oslo=Oslo study I; NCS=Norwegian Counties Study; CONOR=Cohort of Norway; 40-y=Age 40-programme; VHM&PP=Vorarlberg Health Monitoring and Prevention Programme; VIP=Västerbotten Intervention Project; MPP=Malmö Preventive Project; SD=standard deviation; BMI=body mass index.

Table 2: Relative risks (RRs) with 95% confidence intervals (CIs) of blood cancer incidence and mortality by quintiles and Z-scores of individual and combined metabolic factors by sex

		Quintiles, RR (95% CI) ¹					<i>p</i> for trend	Z-score RR ¹ (95% CI)
		1 (ref)	2	3	4	5		
Blood cancer incidence								
All	BMI	1	1.01 (0.87-1.17)	1.14 (0.99-1.31)	1.11 (0.96-1.27)	1.15 (1.00-1.32)	0.051	1.06 (1.02-1.11)
<i>Blood cancer incidence (n=2751)</i>	BP	1	0.87 (0.67-1.11)	0.94 (0.74-1.20)	0.89 (0.70-1.13)	0.95 (0.75-1.20)	0.919	0.98 (0.91-1.05)
	Glucose ²	1	0.96 (0.61-1.51)	0.87 (0.55-1.36)	1.25 (0.81-1.93)	1.15 (0.75-1.77)	0.176	1.05 (0.92-1.20)
	Cholesterol	1	0.81 (0.67-0.99)	0.87 (0.71-1.05)	0.91 (0.76-1.10)	0.72 (0.60-0.87)	0.258	0.90 (0.85-0.95)
	Triglycerides ²	1	1.10 (0.86-1.41)	0.97 (0.75-1.24)	0.91 (0.70-1.16)	0.86 (0.67-1.10)	0.263	0.95 (0.88-1.03)
	MetS score							1.00 (0.94-1.06)
Men								
<i>Blood cancer incidence (n=1710)</i>	BMI	1	1.01 (0.84-1.20)	1.16 (0.98-1.38)	1.09 (0.91-1.29)	1.07 (0.90-1.28)	0.464	1.04 (0.99-1.10)
	BP	1	0.82 (0.60-1.13)	0.88 (0.65-1.19)	0.96 (0.71-1.29)	0.94 (0.70-1.26)	0.934	0.99 (0.90-1.08)
	Glucose ²	1	0.96 (0.55-1.67)	0.71 (0.40-1.26)	1.34 (0.80-2.27)	1.00 (0.59-1.71)	0.726	1.00 (0.85-1.19)
	Cholesterol	1	0.86 (0.67-1.10)	0.86 (0.67-1.10)	0.99 (0.78-1.26)	0.80 (0.63-1.02)	0.360	0.94 (0.87-1.02)
	Triglycerides ²	1	1.19 (0.88-1.61)	0.99 (0.73-1.35)	0.98 (0.72-1.33)	1.02 (0.75-1.39)	0.670	1.00 (0.91-1.10)
	MetS score							1.00 (0.92-1.08)
Women								
<i>Blood cancer incidence (n=1041)</i>	BMI	1	1.02 (0.80-1.32)	1.13 (0.88-1.44)	1.20 (0.94-1.51)	1.35 (1.07-1.71)	0.002	1.12 (1.05-1.19)
	BP	1	0.99 (0.65-1.51)	1.08 (0.71-1.63)	0.86 (0.58-1.30)	1.07 (0.72-1.59)	0.837	0.99 (0.88-1.11)
	Glucose ²	1	0.95 (0.43-2.12)	1.31 (0.62-2.73)	1.08 (0.50-2.31)	1.66 (0.81-3.39)	0.783	1.16 (0.94-1.43)
	Cholesterol	1	0.72 (0.52-1.02)	0.90 (0.65-1.24)	0.85 (0.62-1.17)	0.70 (0.51-0.96)	0.244	0.88 (0.80-0.97)
	Triglycerides ²	1	1.06 (0.69-1.63)	1.02 (0.66-1.57)	0.92 (0.60-1.41)	0.81 (0.53-1.25)	0.025	0.93 (0.82-1.06)
	MetS score							1.01 (0.92-1.12)
Blood cancer mortality								
Men								
<i>Blood cancer mortality (n=730)</i>	BMI	1	0.94 (0.72-1.23)	1.08 (0.83-1.40)	0.95 (0.73-1.24)	1.10 (0.84-1.43)	0.401	1.07 (0.98-1.16)
	BP	1	1.03 (0.62-1.70)	1.08 (0.66-1.76)	1.34 (0.83-2.15)	1.64 (1.03-2.60)	0.008	1.19 (1.03-1.36)
	Glucose ²	1	0.81 (0.36-1.83)	0.35 (0.15-0.84)	0.80 (0.36-1.75)	0.80 (0.36-1.76)	0.758	0.96 (0.73-1.25)
	Cholesterol	1	1.00 (0.68-1.47)	0.90 (0.61-1.32)	1.15 (0.80-1.67)	0.89 (0.61-1.30)	0.800	0.95 (0.84-1.07)
	Triglycerides ²	1	1.14 (0.72-1.81)	1.04 (0.65-1.64)	0.88 (0.55-1.41)	1.11 (0.70-1.77)	0.854	1.04 (0.89-1.21)
	MetS score							1.08 (0.95-1.21)
Women								
<i>Blood cancer mortality (n=340)</i>	BMI	1	1.05 (0.64-1.71)	1.64 (1.06-2.56)	1.14 (0.72-1.80)	1.62 (1.04-2.51)	0.222	1.11 (0.99-1.25)
	BP	1	1.50 (0.66-3.43)	1.45 (0.65-3.25)	1.22 (0.56-2.66)	1.66 (0.77-3.56)	0.196	1.08 (0.89-1.32)
	Glucose ²	1	1.48 (0.37-5.88)	0.94 (0.25-3.53)	1.32 (0.35-4.99)	1.27 (0.36-4.47)	0.601	1.04 (0.71-1.52)
	Cholesterol	1	0.76 (0.41-1.41)	0.78 (0.43-1.41)	0.73 (0.41-1.30)	0.79 (0.45-1.39)	0.336	1.00 (0.84-1.18)
	Triglycerides ²	1	1.01 (0.45-2.26)	1.00 (0.45-2.19)	1.23 (0.57-2.63)	1.30 (0.61-2.77)	0.031	1.16 (0.93-1.44)
	MetS score							1.12 (0.95-1.33)

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¹Stratified by center and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), and corrected for measurement error by RDR

²Normal logarithm transformed measures

Table 3: Relative risks (RRs) with 95% confidence intervals (CIs) of myeloid neoplasms¹ by quintiles and Z-scores of individual and combined metabolic factors by sex

		Quintiles, RR ² (95% CI) ^a						Z-score
		1	2	3	4	5	p for trend	RR ² (95% CI)
Men								
Myeloid neoplasms (n=276)	BMI	1	1.12 (0.71-1.79)	1.13 (0.72-1.79)	1.04 (0.66-1.66)	0.80 (0.49-1.31)	0.219	0.96 (0.83-1.12)
	BP	1	1.02 (0.42-2.46)	1.26 (0.54-2.93)	1.07 (0.46-2.51)	1.33 (0.58-3.03)	0.117	1.11 (0.87-1.41)
	Glucose ³	1	0.91 (0.20-4.15)	0.48 (0.10-2.35)	1.68 (0.41-6.82)	0.72 (0.17-3.18)	0.985	1.18 (0.76-1.85)
	Cholesterol	1	0.49 (0.25-0.96)	0.65 (0.35-1.23)	0.72 (0.39-1.34)	0.50 (0.26-0.96)	0.280	0.89 (0.72-1.10)
	Triglycerides ³	1	0.97 (0.44-2.12)	0.72 (0.32-1.62)	0.69 (0.30-1.55)	0.66 (0.29-1.52)	0.098	0.93 (0.71-1.21)
	MetS score							0.97 (0.79-1.21)
<i>AML (n=144)</i>	BMI	1	0.99 (0.56-1.76)	0.90 (0.50-1.60)	0.83 (0.46-1.48)	0.91 (0.51-1.62)	0.220	1.03 (0.85-1.24)
	BP	1	1.00 (0.33-3.04)	1.21 (0.42-3.49)	1.22 (0.43-3.49)	1.15 (0.40-3.25)	0.250	1.06 (0.78-1.44)
	Glucose ³	1	1.48 (0.21-10.61)	0.91 (0.12-6.94)	3.12 (0.51-19.17)	0.82 (0.12-5.79)	0.888	1.08 (0.61-1.91)
	Cholesterol	1	0.70 (0.30-1.66)	0.85 (0.38-1.94)	0.80 (0.35-1.83)	0.70 (0.31-1.60)	0.225	0.97 (0.75-1.27)
	Triglycerides ³	1	0.80 (0.29-2.24)	0.87 (0.32-2.38)	0.60 (0.21-1.73)	0.86 (0.31-2.39)	0.657	1.03 (0.74-1.44)
	MetS score							1.05 (0.80-1.36)
<i>MPN (n=71)</i>	BMI	1	1.51 (0.65-3.52)	1.63 (0.71-3.74)	1.31 (0.55-3.09)	0.65 (0.24-1.81)	0.428	0.85 (0.64-1.13)
	BP	1	0.95 (0.19-4.82)	1.54 (0.34-6.91)	1.05 (0.22-4.99)	1.52 (0.34-6.80)	0.249	1.17 (0.75-1.81)
	Glucose ³	1	0.65 (0.04-9.96)	0.41 (0.02-7.33)	1.78 (0.15-21.13)	1.06 (0.08-14.17)	0.602	1.57 (0.75-3.30)
	Cholesterol	1	0.12 (0.03-0.51)	0.51 (0.18-1.44)	0.44 (0.15-1.26)	0.31 (0.10-0.95)	0.372	0.75 (0.50-1.11)
	Triglycerides ³	1	1.26 (0.32-5.04)	0.72 (0.16-3.16)	0.96 (0.23-4.02)	0.51 (0.10-2.50)	0.122	0.84 (0.52-1.36)
	MetS score							0.89(0.60-1.31)
Women								
Myeloid neoplasms (n=173)	BMI	1	0.49 (0.24-0.99)	0.93 (0.51-1.69)	0.79 (0.43-1.46)	1.04 (0.58-1.87)	0.626	1.06 (0.88-1.28)
	BP	1	0.95 (0.31-2.92)	0.68 (0.21-2.16)	1.02 (0.35-2.92)	0.86 (0.29-2.49)	0.708	0.93 (0.68-1.27)
	Glucose ³	1	0.79 (0.09-6.85)	0.73 (0.09-5.60)	0.84 (0.11-6.61)	1.11 (0.16-7.77)	0.518	1.22 (0.68-2.18)
	Cholesterol	1	0.67 (0.29-1.52)	0.48 (0.21-1.11)	0.43 (0.19-0.98)	0.25 (0.11-0.59)	0.014	0.67 (0.50-0.88)
	Triglycerides ³	1	3.08 (0.85-11.13)	1.73 (0.46-6.52)	2.03 (0.55-7.42)	1.16 (0.30-4.43)	0.615	0.89 (0.62-1.26)
	MetS score							0.88 (0.67-1.16)
<i>AML (n=87)</i>	BMI	1	0.66 (0.28-1.56)	1.13 (0.54-2.38)	0.69 (0.31-1.55)	0.96 (0.45-2.04)	0.967	0.97 (0.76-1.24)
	BP	1	2.63 (0.57-12.05)	1.03 (0.20-5.39)	2.13 (0.48-9.43)	1.87 (0.42-8.41)	0.654	1.01 (0.69-1.49)
	Glucose ³	1	1.60 (0.10-24.9)	2.09 (0.16-27.01)	1.74 (0.12-24.53)	1.05 (0.08-14.28)	0.935	0.97 (0.45-2.09)
	Cholesterol	1	0.91 (0.32-2.63)	0.67 (0.23-1.96)	0.59 (0.20-1.72)	0.39 (0.13-1.16)	0.003	0.75 (0.53-1.06)
	Triglycerides ³	1	2.22 (0.53-9.35)	0.88 (0.19-4.11)	1.19 (0.27-5.24)	0.54 (0.11-2.59)	0.318	0.75 (0.48-1.16)
	MetS score							0.82 (0.58-1.16)
<i>MPN (n=45)</i>	BMI	1	0.25 (0.06-1.09)	0.70 (0.24-2.04)	1.02 (0.38-2.70)	1.11 (0.42-2.92)	0.466	1.19 (0.87-1.62)
	BP	1	0.18 (0.03-1.27)	0.36 (0.07-1.98)	0.31 (0.06-1.58)	0.29 (0.06-1.49)	0.304	0.82 (0.47-1.44)
	Glucose ³	1	0.26 (0.01- 9.09)	0.10 (0.0-3.39)	0.27 (0.01-7.73)	0.34 (0.01-8.00)	0.359	1.13 (0.40-3.24)
	Cholesterol	1	0.35 (0.09-1.35)	0.29 (0.08-1.11)	0.21 (0.05-0.82)	0.10 (0.02-0.43)	0.072	0.49 (0.30-0.81)
	Triglycerides ³	1	11.1 (0.54-230.4)	10.0(0.48-206.9)	9.93 (0.49-202.9)	5.74 (0.26-124.6)	0.931	1.01 (0.54-1.88)
	MetS score							0.85 (0.52-1.39)

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¹Other myeloid neoplasms N = 83, MDS N=19

²Stratified by center and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), and corrected for measurement error by RDR

³Normal logarithm transformed measures

Acute Myeloid Leukemia (AML), Myeloproliferative Neoplasm (MPN), Myelodysplastic Syndrome (MDS)

- 1 Figure 1a und b Relative risks (RRs) with 95% confidence intervals (CIs) of blood cancer incidence (overall and by main subgroups) and mortality according
- 2 to clinically applied cut-points by sex
- 3
- 4 a) Men
- 5 b) Women

BMI

Systolic blood pressure

Diastolic blood pressure

Table 4: Relative risks (RRs) with 95% confidence intervals (CIs) of lymphoid neoplasms¹ by quintiles and Z-scores of individual and combined metabolic factors by sex

		Quintiles, RR (95% CI) ²						Z-score RR ² (95% CI)
		1	2	3	4	5	p for trend	
Men								
Lymphoid neoplasms combined (n=1292)	BMI	1	0.98 (0.77-1.24)	1.16 (0.92-1.45)	1.12 (0.89-1.41)	1.05 (0.83-1.32)	0.534	1.04 (0.97-1.12)
	BP	1	0.63 (0.41-0.97)	0.80 (0.54-1.19)	0.94 (0.64-1.39)	0.82 (0.56-1.22)	0.886	0.97 (0.86-1.09)
	Glucose ³	1	1.10 (0.52-2.32)	0.88 (0.42-1.88)	1.31 (0.64-2.66)	1.25 (0.61-2.55)	0.247	0.98 (0.78-1.22)
	Cholesterol	1	1.08 (0.78-1.50)	0.88 (0.63-1.22)	0.98 (0.70-1.35)	0.89 (0.64-1.24)	0.298	0.93 (0.84-1.03)
	Triglycerides ³	1	1.35 (0.91-2.00)	1.03 (0.69-1.55)	1.03 (0.69-1.55)	0.96 (0.64-1.46)	0.455	0.95 (0.84-1.09)
	MetS score							0.97 (0.87-1.08)
<i>High B-cell NHL (n=110)</i>	BMI	1	1.02 (0.47-2.24)	1.63 (0.80-3.32)	1.67 (0.82-3.39)	1.96 (0.97-3.96)	0.023	1.31 (1.08-1.59)
	BP	1	1.21 (0.36-4.06)	0.38 (0.10-1.49)	1.09 (0.33-3.60)	1.48 (0.47-4.68)	0.466	1.17 (0.82-1.65)
	Glucose ³	1	1.57 (0.16-15.43)	1.32 (0.13-13.08)	1.69 (0.19-15.19)	2.12 (0.24-18.49)	0.020	1.23 (0.65-2.33)
	Cholesterol	1	1.24 (0.46-3.32)	0.89 (0.32-2.49)	1.38 (0.52-3.62)	1.21 (0.46-3.22)	0.437	0.97 (0.72-1.31)
	Triglycerides ³	1	2.52 (0.73-8.75)	1.94 (0.54-6.95)	1.25 (0.33-4.79)	2.12 (0.58-7.70)	0.681	1.14 (0.78-1.68)
	MetS score							1.31 (0.97-1.77)
<i>Low B-cell NHL (n=407)</i>	BMI	1	1.17 (0.82-1.66)	0.99 (0.70-1.42)	0.95 (0.66-1.36)	1.06 (0.74-1.51)	0.877	1.00 (0.90-1.12)
	BP	1	0.52 (0.26-1.02)	0.94 (0.51-1.72)	0.91 (0.50-1.65)	0.72 (0.39-1.31)	0.658	0.98 (0.81-1.18)
	Glucose ³	1	1.91 (0.63-5.80)	0.86 (0.27-2.76)	0.99 (0.33-3.03)	0.98 (0.32-2.98)	0.637	0.80 (0.56-1.14)
	Cholesterol	1	0.91 (0.55-1.51)	0.83 (0.50-1.37)	0.82 (0.50-1.36)	0.78 (0.47-1.28)	0.023	0.91 (0.77-1.07)
	Triglycerides ³	1	0.91 (0.50-1.68)	1.03 (0.57-1.86)	0.83 (0.45-1.54)	0.60 (0.31-1.14)	0.027	0.84 (0.69-1.03)
	MetS score							0.89 (0.75-1.04)
<i>T-cell NHL (n=46)</i>	BMI	1	0.74 (0.28-1.97)	1.05 (0.43-2.58)	0.60 (0.22-1.65)	0.37 (0.11-1.20)	0.078	0.81 (0.57-1.16)
	BP	1	0.46 (0.10-2.20)	0.33 (0.07-1.65)	0.14 (0.02-0.86)	0.19 (0.03-1.05)	0.090	0.54 (0.29-1.01)
	Glucose ³	1	0.31 (0.01-6.53)	0.08 (0-2.48)	0.64 (0.04-10.37)	0.04 (0-1.47)	0.235	0.44 (0.15-1.36)
	Cholesterol	1	1.88 (0.49-7.16)	0.51 (0.11-2.50)	0.72 (0.16-3.18)	0.43 (0.09-2.11)	0.296	0.66 (0.40-1.08)
	Triglycerides ³	1	0.82 (0.13-4.99)	0.95 (0.16-5.52)	1.34 (0.25-7.30)	0.36 (0.05-2.72)	0.311	0.80 (0.44-1.45)
	MetS score							0.55 (0.34-0.91)
<i>HL (n=104)</i>	BMI	1	0.53 (0.27-1.07)	0.75 (0.40-1.41)	0.73 (0.39-1.38)	0.51 (0.25-1.03)	0.231	0.95 (0.76-1.19)
	BP	1	0.41 (0.12-1.42)	0.57 (0.19-1.76)	0.70 (0.23-2.14)	0.54 (0.17-1.71)	0.451	0.85 (0.58-1.26)
	Glucose ³	1	0.12 (0.01-1.25)	0.12 (0.01-1.27)	0.98 (0.14-6.80)	0.66 (0.09-4.89)	0.076	0.98 (0.49-1.96)
	Cholesterol	1	2.00 (0.71-5.63)	1.07 (0.35-3.26)	1.78 (0.62-5.10)	1.79 (0.63-5.12)	0.393	1.17 (0.87-1.58)
	Triglycerides ³	1	2.11 (0.66-6.73)	0.66 (0.18-2.47)	0.81 (0.23-2.94)	1.43 (0.43-4.80)	0.988	0.97 (0.66-1.43)
	MetS score							0.98 (0.71-1.33)
MM (n=301)	BMI	1	1.00 (0.63-1.60)	1.58 (1.03-2.41)	1.64 (1.07-2.49)	1.27 (0.81-1.98)	0.404	1.06 (0.93-1.21)
	BP	1	0.83 (0.37-1.87)	1.12 (0.53-2.39)	1.50 (0.72-3.11)	1.25 (0.60-2.60)	0.254	1.00 (0.81-1.25)
	Glucose ³	1	1.24 (0.29-5.28)	2.48 (0.63-9.86)	2.48 (0.65-9.41)	3.23 (0.87-12.06)	0.019	1.29 (0.88-1.88)
	Cholesterol	1	0.94 (0.52-1.71)	0.94 (0.52-1.70)	0.94 (0.52-1.69)	0.84 (0.47-1.52)	0.027	0.92 (0.77-1.11)
	Triglycerides ³	1	1.69 (0.82-3.51)	0.96 (0.44-2.07)	1.35 (0.64-2.84)	1.38 (0.65-2.91)	0.725	1.08 (0.86-1.36)

	MetS score							1.07 (0.89-1.28)
Women								
<i>Lymphoid neoplasms combined (n=829)</i>								
	BMI	1	1.23 (0.88-1.73)	1.17 (0.84-1.63)	1.41 (1.03-1.95)	1.55 (1.13-2.13)	0.010	1.15 (1.05-1.25)
	BP	1	1.00 (0.58-1.73)	1.05 (0.61-1.79)	0.73 (0.43-1.25)	0.96 (0.57-1.61)	0.583	0.95 (0.82-1.11)
	Glucose ³	1	0.75 (0.27-2.13)	1.12 (0.43-2.90)	0.81 (0.30-2.21)	1.40 (0.55-3.56)	0.286	1.10 (0.83-1.46)
	Cholesterol	1	0.76 (0.48-1.21)	1.15 (0.76-1.76)	0.90 (0.59-1.39)	0.88 (0.57-1.35)	0.785	0.96 (0.84-1.09)
	Triglycerides ³	1	0.93 (0.53-1.62)	0.86 (0.49-1.50)	0.79 (0.45-1.38)	0.82 (0.47-1.43)	0.138	1.00 (0.85-1.18)
	MetS score							1.06 (0.93-1.20)
<i>High B-cell NHL (n=85)</i>	BMI	1	4.34 (1.46-12.92)	3.55 (1.18-10.72)	2.67 (0.86-8.26)	4.01 (1.35-11.93)	0.366	1.17 (0.93-1.46)
	BP	1	0.57 (0.16-2.04)	0.49 (0.14-1.71)	0.32 (0.09-1.14)	0.31 (0.09-1.09)	0.063	0.72 (0.47-1.10)
	Glucose ³	1	0.36 (0.02-6.75)	0.32 (0.02-5.19)	4.32 (0.37-50.34)	1.86 (0.15-22.53)	0.444	1.74 (0.89-3.40)
	Cholesterol	1	0.32 (0.10-0.99)	0.63 (0.24-1.65)	0.24 (0.08-0.73)	0.34 (0.12-0.95)	0.194	0.79 (0.55-1.12)
	Triglycerides ³	1	0.70 (0.16-3.11)	1.16 (0.28-4.74)	0.96 (0.23-4.00)	0.35 (0.07-1.69)	0.178	0.86 (0.54-1.35)
	MetS score							0.94 (0.67-1.34)
<i>Low B-cell NHL (n=231)</i>	BMI	1	1.24 (0.71-2.15)	1.18 (0.68-2.04)	1.79 (1.07-2.98)	1.49 (0.88-2.52)	0.158	1.16 (1.01-1.33)
	BP	1	0.92 (0.37-2.32)	1.56 (0.66-3.70)	1.05 (0.45-2.49)	0.89 (0.37-2.15)	0.801	0.93 (0.72-1.19)
	Glucose ³	1	0.73 (0.14-3.86)	1.12 (0.24-5.11)	0.75 (0.15-3.70)	0.85 (0.19-3.87)	0.642	0.99 (0.61-1.58)
	Cholesterol	1	1.04 (0.45-2.42)	2.06 (0.97-4.38)	1.66 (0.77-3.58)	1.99 (0.94-4.23)	0.128	1.11 (0.91-1.36)
	Triglycerides ³	1	2.25 (0.87-5.85)	1.28 (0.47-3.46)	1.43 (0.54-3.78)	1.74 (0.67-4.53)	0.725	1.07 (0.82-1.40)
	MetS score							1.12 (0.91-1.37)
<i>T-cell NHL (n=24)</i>	BMI	1	0.86 (0.22-3.45)	0.81 (0.20-3.24)	0.74 (0.18-3.02)	0.59 (0.13-2.62)	0.009	0.80 (0.47-1.34)
	BP	1	0.21 (0.02-2.52)	0.18 (0.01-2.24)	0.44 (0.05-3.57)	0.31 (0.03-2.86)	0.389	0.70 (0.31-1.56)
	Glucose ³	1	0.03 (0.00-14.70)	0.84 (0.01-68.34)	0.10 (0.00-19.23)	1.81 (0.03-120.3)	0.431	1.43 (0.36-5.69)
	Cholesterol	1	0.27 (0.03-2.18)	0.50 (0.08-3.09)	0.45 (0.07-2.84)	0.38 (0.06-2.52)	0.298	0.69 (0.35-1.36)
	Triglycerides ³	1	0.60 (0.06-5.89)	0.54 (0.05-5.38)	0.34 (0.03-3.88)	-	0.075	0.33 (0.15-0.72)
	MetS score							0.56 (0.27-1.14)
<i>HL (n=70)</i>	BMI	1	1.10 (0.37-3.33)	1.25 (0.44-3.57)	1.46 (0.53-4.02)	2.38 (0.91-6.23)	0.015	1.40 (1.12-1.74)
	BP	1	1.39 (0.23-8.41)	0.63 (0.09-4.56)	1.09 (0.18-6.48)	2.74 (0.50-15.13)	0.146	1.49 (0.98-2.25)
	Glucose ³	1	1.23 (0.07-22.27)	0.36 (0.02-7.04)	1.46 (0.09-23.60)	0.67 (0.04-10.82)	0.758	0.91 (0.39-2.11)
	Cholesterol	1	0.91 (0.23-3.58)	0.96 (0.26-3.58)	0.89 (0.24-3.28)	1.17 (0.33-4.16)	0.351	1.01 (0.69-1.46)
	Triglycerides ³	1	0.12 (0.01-0.96)	0.77 (0.16-3.79)	0.85 (0.18-4.08)	1.49 (0.34-6.65)	0.191	1.62 (1.02-2.56)
	MetS score							1.48 (1.05-2.09)
<i>MM (n=196)</i>	BMI	1	0.85 (0.48-1.50)	0.84 (0.48-1.47)	0.98 (0.57-1.66)	1.17 (0.70-1.97)	0.280	1.07 (0.92-1.25)
	BP	1	1.89 (0.69-5.22)	1.54 (0.56-4.28)	0.80 (0.28-2.24)	1.62 (0.61-4.30)	0.818	0.96 (0.73-1.25)
	Glucose ³	1	1.18 (0.19-7.57)	2.52 (0.47-13.46)	0.3 (0.04-2.12)	2.72 (0.53-14.04)	0.438	1.04 (0.63-1.71)
	Cholesterol	1	0.99 (0.45-2.19)	1.12 (0.53-2.38)	1.02 (0.48-2.16)	0.60 (0.27-1.31)	0.190	0.87 (0.69-1.10)
	Triglycerides ³	1	0.68 (0.26-1.79)	0.57 (0.21-1.50)	0.43 (0.16-1.16)	0.56 (0.22-1.45)	0.275	0.94 (0.70-1.26)
	MetS score							0.98 (0.78-1.23)

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¹Other lymphoid neoplasms N=547

²Stratified by center and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), and corrected for measurement error by RDR

³Normal logarithm transformed measures

High and low grade B-cell lymphoma (high and low B-cell -NHL), T-cell lymphoma (T-cell NHL), Hodgkin Lymphoma (HL) and Multiple Myeloma (MM).