Racial differences in the proportion of myeloma cases attributable to excess body weight and diabetes mellitus in the United States

Multiple myeloma (MM) is a hematologic malignancy that disproportionately affects Black populations. In the US, Black individuals are twice as likely to be diagnosed with MM compared to their White counterparts.[1] This disparity can be attributed to a combination of genetic, socio-environmental and lifestyle factors. Notably, modifiable risk factors such as elevated body mass index (BMI) and diabetes mellitus (DM) have been identified as risk factors for MM.[2-4] MM is one of 13 cancers associated with obesity.[5] The prevalence of obesity and DM is also higher in non-Hispanic Black (NHB) and Hispanic adults than in non-Hispanic White (NHW) adults.[6]

Recent studies have highlighted concerning trends in MM incidence. For instance, the incidence of MM has risen among young adults in the United States (US).[7] Globally, MM incidence has shown an increasing trend over the past several decades,[8] with this rise paralleling an increase in obesity prevalence. This pattern is consistent with research indicating that obesity is a risk factor for MM, and may be driven by multiple mechanisms such as chronic inflammation where stressed adipocytes and fat-infiltrating immune cells secrete adipokines and inflammatory cytokines which facilitate MM expansion.[9] Similarly, DM is also considered as a risk factor for MM with possible mechanisms including hyperinsulinemia, hyperglycemia, inflammation, immune suppression, and increased insulin-like growth factor.[3,10]

As obesity and DM rates continue to rise in the US and worldwide, its effect on incidence of obesity-related neoplasms such as MM, make it important to estimate the percentage of MM cases attributed to elevated BMI and DM. Additionally, given the differences in MM risk by race, we further evaluated the contribution of these modifiable risk factors by racial groups. Therefore, our study aims to quantify the proportion of MM cases attributable to these modifiable risk factors among adults aged 18 and older. We calculated the population attributable fraction (PAF) which is an estimate of the proportion of cases attributable to elevated BMI or DM overall and for NHW, NHB, and Hispanics.[11]

This study was conducted using de-identified, publicly available data and did not require institutional review board approval or patient written consent. It respects the ethical research guidelines and considerations set out in the US. The number of MM cancer cases from 2016 to 2021 in the US, including stratification by age, race, and ethnicity, was obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[1]

Data on prevalence of overweight (BMI: 25-30 kg/m^2) and obese (BMI: ≥30 kg/m^2) BMI and DM per race for age groups 18-44, 45-64, 65-74 and 75+ years from 2006-11 was obtained from the Integrated Public Use Microdata Series (IPUMS) Health Surveys database which harmonizes the National Health Interview Survey (NHIS) data provided by the National Center for Health Statistics (*Online Supplementary Table S1*).[6,12] NHIS is a survey collecting information on the health, health care access, and health behaviors of the civilian, non-institutionalized US population, with digital data files available from 1963 to the present day. We used the 2006-to-2011 time frame to allow for an approximate 10-year lag period between BMI and DM prevalence and MM occurrence based on prior literature[11] given similar rate of progression from MGUS to MM by race/ethnicity.[13]

We calculated the PAF of incident MM cases attributable to BMI and DM based on hazard ratio (HR) estimates from two large epidemiologic studies evaluating MM risk with elevated BMI in the NIH AARP Diet and Health Study and DM using healthcare databases from Ontario, Canada.[2,3] The estimate of MM risk for overweight HR 1.09 (95% Confidence Interval [CI]: 0.82-1.47) was used. For obesity, the lower range estimates HR 1.26 (95% CI: 1.01-1.64) based on BMI 30-34.9 kg/m^2 and upper range estimates HR 1.55 (95% CI: 1.01-2.39) based on BMI ≥35 kg/m^2 for MM risk were used. CI were set to have the same *P* value as reported for BMI ≥35 kg/m^2 patients.[2] For elevated BMI, we utilized two estimates: BMI PAF_{BMI30} (overweight and lower range obesity HR estimates) and BMI PAF_{BMI35} (overweight and upper range obesity HR estimates). The estimate of MM risk for DM HR 1.15 (95% CI: 1.09-1.23) was used. The race and age-specific PAF with corresponding 95% CI were estimated using 10,000 parametric bootstrap replications based on the above HR, BMI or DM prevalence, and corresponding standard errors estimated from NHIS data.

Across all age groups, NHB and Hispanic populations have higher obesity rates compared to NHW populations (*Online Supplementary Table S1*). For example, in the 45-64 year-old age group, obesity affected 44% of NHB, 37.5% of Hispanics and 34% of NHW whereas for those aged 65-74 years, rates were 41.9% in NHB, 36.3% in Hispanics and 32.3% in NHW (*Online Supplementary Table S1*). The PAF_{BMI30} for MM cases attributable to elevated BMI is 10.8%

Table 1. Estimated number of multiple myeloma cases attributable to elevated body mass index and diabetes mellitus in adults aged 18 years or older, 2016-2021.

Annual MM cases	Parameters	All races	NHW	NHB	Hispanic
Overall estimate	Cases, N	29,320	18,765	6,298	4,257
Elevated BMI (lower range) estimate	PAF_{BMI30}% 95% CI Cases, N	10.8 -1.0 to 22.0 3,178	10.5 -1.0 to 21.8 1,963	12.7 0.0 to 24.7 800	11.7 -1.0 to 23.7 496
Elevated BMI (upper range) estimate	PAF_{BMI35}% 95% CI Cases, N	17.1 0.3 to 31.7 5,026	16.3 0.8 to 31.3 3,063	20.0 1.5 to 37.3 1,261	18.1 0.8 to 34.2 769
Diabetes mellitus estimate	PAF_{DM}% 95% CI Cases, N	1.2 1.0 to 1.8 345	1.1 1.0 to 1.8 207	1.7 1.0 to 2.2 106	1.2 1.0 to 2.0 52

The estimated proportion and average number (N) of multiple myeloma (MM) cases attributable to elevated body mass index (BMI) and diabetes mellitus across different racial and ethnic groups. The population attributable fraction (PAF) and corresponding 95% Confidence Intervals (CI) are reported for BMI-related risk estimates based on hazard ratios corresponding to the lower and upper ranges of obesity (PAF_{BMI30} and PAF_{BMI35}, respectively), as well as for diabetes mellitus-related risk estimates (PAF_{DM}). The number of attributable cases is calculated for each category, and total cases are provided for all racial and ethnic groups, including non-Hispanic White (NHW), non-Hispanic Black (NHB), and Hispanic populations. All races: aggregate of NHW + NHB + Hispanic.

(95% CI: -1.0-22.0%) overall, 12.7% (95% CI: 0.0-24.7%) in NHB, 11.7% (95% CI: -1.0-23.7%) in Hispanics, and 10.5% (95% CI: -1.0-21.8%) in NHW (Table 1, Figure 1A, *Online Supplementary Table S2*). Whereas the PAF_{BMI35} is 17.1% (95% CI: 0.3-31.7%) overall, 20.0% (95% CI: 1.5-37.3%) in NHB, 18.1% (95% CI: 0.8-34.2%) in Hispanics and 16.3% (95% CI: 0.8-31.3%) in NHW (Table 1, Figure 1B, *Online Supplementary Table S2*). Therefore, an additional 2.3-3.7% of MM cases in NHB and an additional 1.2-1.8% of MM cases in Hispanics may be attributable to elevated BMI when compared to NHW.

Similarly, DM prevalence was significantly higher in NHB populations compared to NHW populations across all age groups, with a greater increase observed in NHB as age advanced. For example, in the 45-64 age group rates were 17.0% in NHB, 17.1% in Hispanics *versus* 9.9% in NHW, and for ages 65-74 it was 31.1% in NHB, 29.3% in Hispanics and 16.5% in NHW (*Online Supplementary Table S1*). These findings highlight a significantly higher proportion of DM in NHB and Hispanics. The PAF_{DM} of MM cases being attributable to DM is 1.2% (95% CI: 1.0-1.8%) overall, 1.7% (95% CI: 1.0-2.2%) in NHB, 1.2% (95% CI: 1.0-2.0%) in Hispanics and 1.1% (95% CI: 1.0-1.8%) in NHW (Table 1, Figure 1C, *Online Supplementary Table S3*). Thus, an additional 0.6% of MM cases in NHB and an additional 0.1% of MM cases in Hispanics may be attributable to DM compared to NHW.

We applied these findings to estimate the annual number of MM cases that were attributable to elevated BMI and DM. We estimate there were 31,780[14] average newly diagnosed MM cases annually in the US between 2016-2021 of which 29,320 cases were in NHW, NHB and Hispanics. Of these MM cases, at least 3,178 (PAF_{BMI30} = 10.84%) and up to 5,026 (PAF_{BMI35} = 17.14%) cases were attributable to an elevated BMI. In NHW there were between 1,963-3,063 cases out of 18,765 cases (PAF_{BMI30} = 10.46%; PAF_{BMI35} = 16.32%), in NHB there were between 800-1,261 cases out of 6,298 cases (PAF_{BMI30} = 12.7%; PAF_{BMI35} = 20.0%), and in Hispanics there were between 496-769 cases out of 4,257 (PAF_{BMI30} = 11.66%; PAF_{BMI35} = 18.06%) attributable to an elevated BMI (Table 1). Similarly, up to 345 (PAF_{DM} = 1.18%) cases were attributable to DM. In NHW, there were 207 cases out of 18,765 cases (PAF_{DM} = 1.1%), in NHB, there were 106 cases out of 6,298 cases (PAF_{DM} =1.7%), and in Hispanics, there were about 52 cases out of 4,257 cases (PAF_{DM} = 1.2%) attributable to DM (Table 1). These findings suggest that preventive methods could be successful in decreasing the incidence of MM.

Strengths of this analysis include utilizing risk estimates from large epidemiologic studies and data from national publicly available datasets and a 5-year period over which we assessed risk with an estimated 10-year lag time to account for time from metabolic disorder to MM diagnosis. Some limitations include the estimates utilized being limited by available research with wide CI, elevated BMI and DM status are self-reported so they may be under-reported, and prediabetes may also increase risk and was not included in the estimates. BMI and DM have been analyzed as separate conditions, as it was not possible to conduct an interaction analysis for those with a concomitant diagnosis of elevated BMI and DM with the available data. All races were also not included and therefore the absolute number of cases attributable to these risk factors is likely an underestimate. While elevated BMI and DM contribute to a substantial proportion of the increased risk of MM overall, it does not fully account for the two times higher incidence in NHB compared to NHW. These findings suggest a need for researching compre-

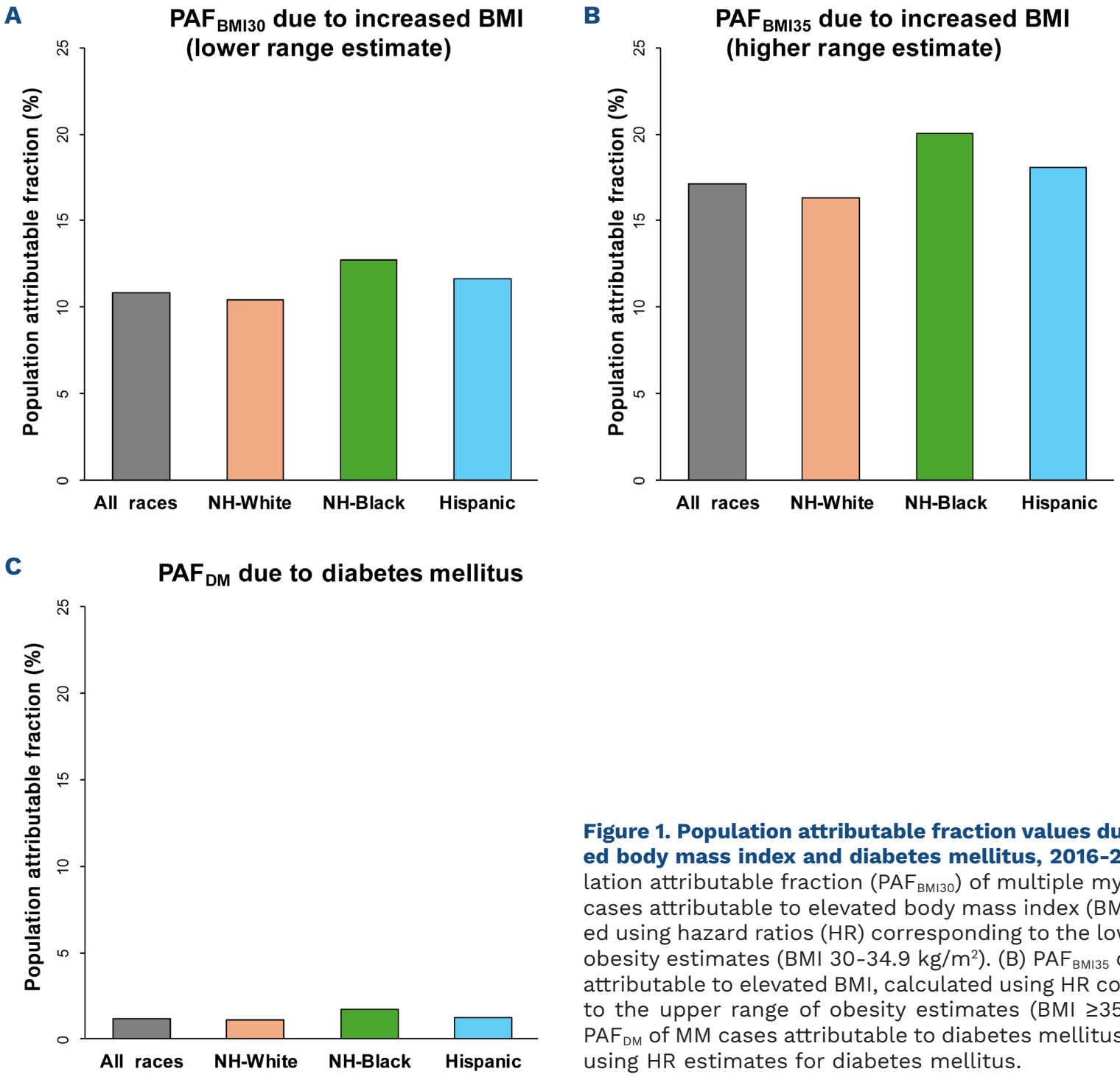

Figure 1. Population attributable fraction values due to elevated body mass index and diabetes mellitus, 2016-21. (A) Population attributable fraction (PAF_{BMI30}) of multiple myeloma (MM) cases attributable to elevated body mass index (BMI), calculated using hazard ratios (HR) corresponding to the lower range of obesity estimates (BMI 30-34.9 kg/m^2). (B) PAF_{BMI35} of MM cases attributable to elevated BMI, calculated using HR corresponding to the upper range of obesity estimates (BMI ≥35 kg/m^2). (C) PAF_{DM} of MM cases attributable to diabetes mellitus, calculated using HR estimates for diabetes mellitus.

hensive lifestyle intervention strategies to lower BMI and reduce DM incidence among the general population. Dietary trials such as NUTRIVENTION (clinicaltrials.gov NCT04920084 and NCT05640843) are evaluating whether strategies such as high fiber, plant-based diets that reduce weight, insulin resistance and improve microbiome composition and inflammation may delay progression from monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) to MM, and early evidence suggests this may be possible in certain cases.[15] Drug strategies such as the glucagon-like peptide 1 receptor agonists (GLP-1RA) are being used widely for weight and DM management. They have been associated with reduced risk of obesity-related cancers such as MM when compared with insulin or metformin in patients with type 2 DM[16] although interventional trials for cancer risk reduction are lacking. Thus, drugs such as GLP-1RA and lifestyle strategies such as fiber rich diets highlight potential strategies for MM risk reduction to reduce the significant financial, emotional, and social burden of this diagnosis.

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Contributions

AA and DR collected data, performed the analysis, and wrote the manuscript with support from UAS. AD contributed to data and analysis tools, and performed the analysis. SZU contributed to manuscript review and revision. UAS conceived the study concept and designed the analysis. All authors reviewed and revised the final manuscript for publication.

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Data-sharing statement

The data used in this manuscript are publicly available.

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