Original Article

JOURNAL OF MULTIMORBIDITY & COMORBIDITY

Journal of Multimorbidity and Comorbidity
Volume 13: 1–10

DOI: 10.1177/26335652311601 39
journals.sagepub.com/home/cob
SAGE

Synergistic interactions of obesity with sex, education, and smoking and accumulation of multi-morbidity (MM) across the lifespan

Jennifer L St Sauver, PhD, MPH[1,2], Brandon R Grossardt, MS[3], Alanna M Chamberlain, PhD, MPH[1,4], Ekta Kapoor, MBBS[6,7,8,9,10] and Walter A Rocca, MD, MPH[1,5,6]

Abstract

Objectives: Obesity is a potentially modifiable risk factor that has been consistently associated with the development and progression of multi-morbidity (MM). However, obesity may be more problematic for some persons compared to others because of interactions with other risk factors. Therefore, we studied the effect of interactions between patient characteristics and overweight and obesity on the rate of accumulation of MM.

Methods: We studied 4 cohorts of persons ages 20-, 40-, 60-, and 80-years residing in Olmsted County, Minnesota between 2005 and 2014 using the Rochester Epidemiology Project (REP) medical records-linkage system. Body mass index, sex, race, ethnicity, education, and smoking status were extracted from REP indices. The rate of accumulation of MM was calculated as the number of new chronic conditions accumulated per 10 person years through 2017. Poisson rate regression models were used to identify associations between characteristics and rate of MM accumulation. Additive interactions were summarized using relative excess risk due to interaction, attributable proportion of disease, and the synergy index.

Results: Greater than additive synergistic associations were observed between female sex and obesity in the 20- and 40-year cohorts, between low education and obesity in the 20-year cohort (both sexes), and between smoking and obesity in the 40-year cohort (both sexes).

Conclusions: Interventions targeted at women, persons with lower education, and smokers who also have obesity may result in the greatest reduction in the rate of MM accumulation. However, interventions may need to focus on persons prior to mid-life to have the greatest effect.

[1]Division of Epidemiology, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA
[2]The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, USA
[3]Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA
[4]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA
[5]Department of Neurology, Mayo Clinic, Rochester, MN, USA
[6]Women's Health Research Center, Mayo Clinic, Rochester, MN, USA
[7]Menopause and Women's Sexual Health Clinic, Division of General Internal Medicine, Mayo Clinic, Rochester, MN, USA
[8]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, MN, USA
[9]Center for Women's Health, Mayo Clinic, Rochester, MN, USA
[10]Menopause and Women's Sexual Health Clinic, Mayo Clinic, Rochester, MN, USA

Corresponding author:
Jennifer L. St Sauver, PhD, MPH, Division of Epidemiology, Department of Quantitative Health Sciences, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.
Email: stsauver.jennifer@mayo.edu

Keywords
obesity, body mass index, clinical research, epidemiology, multi-morbidity

Received 19 October 2022; accepted: 3 February 2023

Introduction

A combination of biologic factors, lifestyle behaviors, and social determinants of health may cause physical changes that lead to multi-morbidity (MM) and a reduced health and life span.[1, 2] Obesity is a potentially modifiable risk factor that has been consistently associated with both prevalent MM, and with the development and progression of MM over time.[3-7] However, obesity may be more problematic for some persons compared to others because of interactions with other risk factors.

Interaction analyses can be used to determine whether persons with two or more risk factors are at a greater risk of a particular outcome than would be expected due to the independent effects of each factor alone.[8] In particular, studies of greater-than-additive ("super-additive") interactions may be especially relevant for clinical and public health decisions.[9] However, few studies have examined whether interactions between patient characteristics and obesity increase the risk of developing specific chronic diseases of aging more than would be expected. Luo and colleagues found that smoking and obesity interacted to increase the odds of self-reported cardiovascular disease, but not the risk of type 2 diabetes in Chinese populations.[10, 11] Saadati and colleagues found that age, but not sex, modified the association between higher body mass index (BMI) and risk of coronary heart disease.[12]

Even fewer studies have examined the effect of interacting variables on the accumulation of MM. In a cross-sectional analysis, age and sex interacted with BMI, such that elderly Brazilian women with obesity had a greater than expected likelihood of having MM.[13] By contrast, in a cohort study, Botoseneanu and colleagues found that middle aged Black persons had a higher initial burden of MM and a more rapid rate of accumulation of chronic conditions over time compared to White and Hispanic persons.[7] However, interactions between BMI and race were not significant, suggesting that race and BMI exert independent effects on the accumulation of MM.

These limited studies represent a mix of study designs, most are cross-sectional, and only two have examined MM as an outcome. However, these studies suggest that smoking, age, and sex are important variables to study in combination with BMI to identify persons at highest risk for accumulating MM. Therefore, we hypothesized that BMI interacts with other MM risk factors greater-than-additively (synergistically) to increase the rate of MM. Identification of the persons at an unexpectedly high risk of MM may help target preventive and therapeutic interventions to those who are most likely to benefit from them. To address this question, we studied the effect of several participant characteristics (age, sex, race, ethnicity, education level, and smoking status) combined with BMI on the rate of accumulation of MM in a large Midwestern population.

Methods

Data Source and Study Population

The Rochester Epidemiology Project (REP) medical records-linkage system was used to identify residents of Olmsted County, Minnesota between 1 Jan 2005 and 31 Dec 2014. Details about the REP have been previously reported.[14-16] Briefly, the REP links medical record data from local health care providers for virtually all persons residing in Olmsted County, MN.[15, 16] Olmsted County is geographically isolated from other cities with other health care providers, and the REP includes information from the major health care providers in the county, which provide primary, secondary, and tertiary care. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. The study was deemed minimal risk by both Boards and the requirement for informed consent was waived. However, we note that we excluded persons who did not provide authorization for their records to be used for research, as per Minnesota statute (<5%).[14] We also excluded persons who did not reach at least one birthday during the study period (<5%).

The sample was divided into 4 cohorts anchored at birthday ages of 20, 40, 60, and 80 years. These 4 cohorts were chosen to represent young, middle-aged, older, and elderly populations. The 20-year-old cohort included all persons who celebrated their 20th birthday as Olmsted County residents between 1 Jan 2005 and 31 Dec 2014. These persons were followed from the date of their 20th birthday (index date) through the end of the study, defined as the earliest of three dates: the date of death, the date of last medical contact with the REP, or 31 Dec 2017 (to allow for at least 3 years of follow-up after the index date). The remaining age cohorts were similarly defined. We excluded persons who did not have any diagnostic codes in at least 2 of the 5 years prior to the anchoring birthdate (index date). These persons were considered to have insufficient medical information to adequately assess the presence or absence of prevalent chronic conditions. A flowchart of the four study cohorts is shown in Supplemental Figure 1.

Obesity Categories

Information on BMI at index date was extracted from the REP electronic indices.[16] BMI was categorized into 3 strata: normal (18.5 to < 25.0 kg/m^2), overweight (25.0 to < 30.0 kg/m^2), and obese (≥30.0 kg/m^2). We excluded persons who were underweight, because this category included both persons who were healthy but below normal weight, and persons who were underweight due to an underlying condition.[17]

Patient Characteristics

Age at cohort entry was fixed by design to index birthdays at ages 20, 40, 60, and 80 years. Information on sex, self-reported race (White, Black, Asian, Other/mixed), and ethnic group (Hispanic, non-Hispanic), self-reported education level, and smoking status were electronically extracted from REP indices for all cohort members.[16] Education level was categorized as high school or less and more than high school, and smoking status was categorized as never smoker and ever smoker (former or current).

Accumulation of Chronic Conditions

The primary endpoint was the rate of accumulation of newly diagnosed chronic conditions. We considered 20 chronic conditions recommended by the US Department of Health and Human Services for studies of MM (Supplemental Table 1).[18]

The presence of each chronic condition was defined based on having two or more ICD-9 or ICD-10 diagnostic codes for a given condition separated by more than 30 days. We have previously shown that this definition results in a higher positive predictive value for identifying chronic conditions compared to using a single diagnosis code.[19] The date of onset of a given condition was defined as the date of the earliest diagnosis code that occurred more than 30 days after the first corresponding diagnosis code (date of second qualifying code).

The rate of accumulation of conditions was calculated as the number of new MM conditions accumulated per 10 person years. To account for conditions present at index date, we used a scaled (weighted) number of conditions. Specifically, each accumulated new condition after the index date was weighted so that each person's maximum attainable new accumulated conditions total was 20. Therefore, for persons with zero conditions at baseline, each accumulated condition was counted as 1.0 new conditions in the numerator for the rate calculations. However, for a person with two prevalent MM conditions, each new incident MM condition was weighted as 1.11 conditions in the numerator for the rate calculation (1.11 = 20 divided by 18). This scaled calculation ensured that all persons in our study were able to contribute up to 20 conditions to the numerator.

Data Analyses

All analyses were completed separately for the 4 birthday cohorts. Personal characteristics were summarized using counts and percentages or median and 25th and 75th percentiles. The rate of MM accumulation was calculated using the number of scaled new MM conditions divided by the cumulative person-years under observation. Rates were multiplied by 10 (rate per 10 person-years) for ease of interpretation, and as recommended for epidemiology studies.[20] Poisson regression models were fit using the scaled new MM conditions as the numerator and person-years as the denominator. For completeness, the full multivariable Poisson models included the "unknown" categories for race, education level, and smoking status groups.

Tests of synergistic additive interaction between overweight and obese separately and other personal characteristics were performed using the SAS code provided by Lundberg et al.[21] The results were summarized using relative excess risk due to interaction (RERI), attributable proportion of disease among those with both exposures due to interaction (AP), and the synergy index (SI). Interaction analysis models included all personal characteristics other than BMI category as adjustment variables. For example, in the interaction analysis between BMI (obese vs. normal) and sex (men vs. women), the model included adjustment variables for race, ethnicity, education level, and smoking status (Supplemental Figure 2A). Similarly, in the interaction analysis between BMI and smoking status (ever vs. never), the model included adjustment variables for sex, race, ethnicity, and education level (Supplemental Figure 2B). All rates and estimates of risk ratios (RR) are reported with 95% confidence intervals. All statistical tests were performed using SAS version 9.4 (Cary, NC) at a two-tailed alpha level of 0.05.

Results

The 4 age cohorts differed in characteristics at index date (Table 1). The proportion of persons with obesity was lowest in the 20-year age cohort (13.8%) and highest in the 60-year age cohort (41.8%). Persons in the 20-year age cohort were more racially diverse than persons in the 80-year age cohort (85% white vs 95% white; Table 1).

Persons in the 80-year cohort were most likely to have less than a high school education (45%), and to have been a former or current smoker (57%) compared to the other cohorts (Table 1). Finally, older persons had more prevalent chronic conditions at index date, and accumulated more new conditions during follow-up than younger persons (Table 1). The median follow-up time for all cohorts was

Table 1. Descriptive information for cohorts anchored at ages 20, 40, 60, and 80 years.

	Birthday age cohort				
	20-year	40-year	60-year	80-year	All persons
Characteristic	N = 14,489	N = 13,402	N = 12,893	N = 5,248	N = 46,032
BMI category*					
Normal	9,223 (63.7)	4,117 (30.7)	2,855 (22.1)	1,406 (26.8)	17,601 (38.2)
Overweight	3,273 (22.6)	4,542 (33.9)	4,653 (36.1)	2,186 (41.7)	14,654 (31.8)
Obese	1,993 (13.8)	4,743 (35.4)	5,385 (41.8)	1,656 (31.6)	13,777 (29.9)
Sex					
Women, N (%)	7,590 (52.4)	7,358 (54.9)	6,855 (53.2)	2,903 (55.3)	24,706 (53.7)
Men, N (%)	6,899 (47.6)	6,044 (45.1)	6,038 (46.8)	2,345 (44.7)	21,326 (46.3)
Race					
White, N (%)	12,314 (85.0)	11,292 (84.3)	11,884 (92.2)	5,001 (95.3)	40,491 (88.0)
Black, N (%)	787 (5.4)	599 (4.5)	227 (1.8)	59 (1.1)	1,672 (3.6)
Asian, N (%)	563 (3.9)	756 (5.6)	420 (3.3)	105 (2.0)	1,844 (4.0)
Other / mixed, N (%)†	652 (4.5)	634 (4.7)	292 (2.3)	76 (1.4)	1,654 (3.6)
Unknown, N (%)	173 (1.2)	121 (0.9)	70 (0.5)	7 (0.1)	371 (0.8)
Ethnicity					
Non-Hispanic, N (%)	13,756 (94.9)	12,668 (94.5)	12,470 (96.7)	5,180 (98.7)	44,074 (95.7)
Hispanic, N (%)	733 (5.1)	734 (5.5)	423 (3.3)	68 (1.3)	1,958 (4.3)
Education level					
High school or less, N (%)	3,033 (20.9)	1,733 (12.9)	2,522 (19.6)	2,346 (44.7)	9,634 (20.9)
More than high school, N (%)	7,900 (54.5)	10,111 (75.4)	9,478 (73.5)	2,760 (52.6)	30,249 (65.7)
Unknown, N (%)	3,556 (24.5)	1,558 (11.6)	893 (6.9)	142 (2.7)	6,149 (13.4)
Smoking status					
Never, N (%)	6,945 (47.9)	5,862 (43.7)	4,840 (37.5)	1,750 (33.3)	19,397 (42.1)
Ever (former or current), N (%)	2,784 (19.2)	4,903 (36.6)	6,341 (49.2)	2,996 (57.1)	17,024 (37.0)
Unknown, N (%)	4,760 (32.9)	2,637 (19.7)	1,712 (13.3)	502 (9.6)	9,611 (20.9)
Prevalent MM conditions, med. (Q1, Q3)	0 (0, 1)	0 (0, 1)	2 (1, 3)	4 (2, 5)	1 (0, 2)
Follow-up information					
Follow-up years, med. (Q1, Q3)	5.9 (3.8, 8.6)	7.4 (4.9, 10.0)	6.8 (4.6, 9.6)	5.9 (3.9, 8.4)	6.6 (4.3, 9.3)
Incident MM conditions, med. (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 1.2)	1.3 (0.0, 3.0)	2.7 (1.3, 4.7)	1.0 (0.0, 2.1)

BMI = body mass index; med. = median (50th percentile); MM = multi-morbidity; Q1 = first quartile (25th percentile); Q3 = third quartile (75th percentile).
*BMI categories are defined using standard cut-offs of Normal BMI (< 25 kg/m^2), Overweight BMI (25 to <30 kg/m^2), and Obese BMI (≥ 30 kg/m^2).
†Persons included in the race category of "Other / mixed" are those who self-reported a race other than White, Black, or Asian (e.g., American Indian) or persons who self-reported race as "mixed race" or "two or more races."

6.6 years, and follow-up time differed slightly across the age cohorts (Table 1).

Rates of accumulation of new chronic conditions in each age cohort and across 3 BMI categories (normal, overweight, and obese) are shown in Figure 1 and Table 2. Persons in older age cohorts accumulated new chronic conditions at a faster rate than persons in younger age cohorts. Similarly, persons who were overweight or had obesity accumulated new chronic conditions at a faster rate than persons who were normal weight in every age cohort (Figure 1). For example, in the 40-year age cohort, persons with normal weight accumulated <1 new condition per 10 person-years. Persons who were overweight accumulated 1.2 new conditions, and persons with obesity accumulated 1.8 new conditions per 10 person-years.

After adjusting for sex, race, ethnicity, education level, and smoking status, obese status was associated with an increased rate of accumulation of MM in all age cohorts (Table 2, adjusted RRs). The association between obesity and the rate of accumulation of MM was strongest in the 40-year-old cohort (RR: 2.05, 95% CI: 2.01, 2.10), and weakest in the 80-year-old cohort (RR: 1.16, 95% CI: 1.12, 1.20). Results were similar for overweight status, but were not statistically significant in the 80-year-old age cohort. Similarly, a high school education or less and former or current smoking status were consistently associated with a higher rate of MM accumulation across all 4 age cohorts (Table 2).

By contrast, associations between sex, race, ethnicity and accumulation of MM differed across age groups. Female

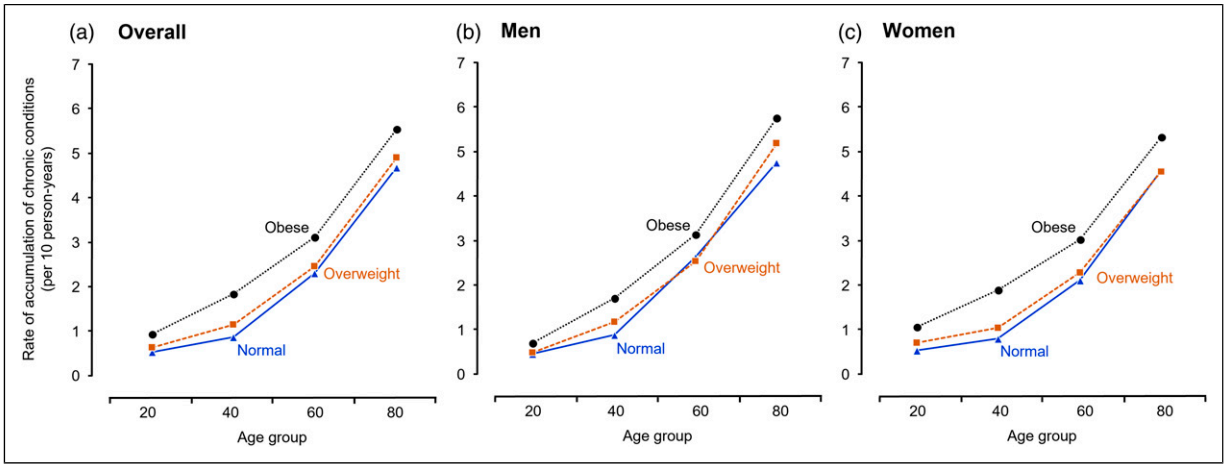

Figure 1. Rate of accumulation of chronic conditions per 10 person years by age group overall (Panel A), in men (Panel B), and in women (Panel C).

sex was associated with an increased rate of accumulation of chronic conditions in the 20-year age cohort, sex was not associated with MM rate in the 40-year age cohort, and male sex was associated with an increased MM rate in the 60 and 80-year cohorts (Table 2). Black race was consistently associated with a higher MM rate in the 20-, 40-, and 60-year age cohorts. By constrast, Asian race was associated with a lower MM rate in the 20-year age cohort, but with a higher MM rate in the 60-year age cohort. Hispanic ethnicity was associated with a higher MM rate in the 20-year cohort, but with a lower MM rate in the 40- and 60-year cohorts (Table 2).

Supplemental Table 2 shows the results of additive interaction analyses of BMI status with sex (Supplemental Table 2A), Black vs. White race (2B), Asian vs. White race (2C), Hispanic ethnicity (2D), lower education (2E), and smoking status (2F). Although Black and Asian race and Hispanic ethnicity were associated with a faster rate of accumulation of chronic conditions in some of the age groups (Table 2), these characteristics did not interact significantly with BMI status to increase the risk of MM (Supplemental Tables 2B, 2C, and 2D). The single exception was a significant synergistic interaction between Asian race and being overweight in the 40-year age cohort (Supplemental Table 2C).

Sex, education, and smoking status interacted greater than additively with obesity to increase the rate of MM accumulation (Figure 2, Supplemental Tables 2A, 2E, and 2F). However, these associations differed depending on the age of the cohort. For example, in the 20-year age cohort, women who were overweight or who had obesity had a greater than additive increased risk of accumulating MM compared to men with a normal BMI (Figure 2, Panel A, red asterisk values). Significant additive interactions between female sex and obesity were also observed in the 40-year age cohort.

Persons with low education and obesity were at highest risk for accumulation of MM in all age groups (Figure 2, Panel B, right side) compared to persons of normal BMI with higher education. However, the interaction between BMI status and education level was statistically significant only for persons in the 20-year age cohort. Persons who ever smoked and had obesity were also consistently at highest risk for accumulation of MM compared to non-smokers of normal weight in all age groups (Figure 2, Panel C, right side). However, the interaction between obesity and smoking status was statistically significant only for persons in the 40-year age cohort.

Discussion

We found that female sex, lower education, and smoking status interacted significantly with obesity to increase the risk of accumulating MM more rapidly than would be expected by adding the individual effects together (i.e., super-additive or synergistic effects). However, the interaction effects differed across the lifespan. Finally, the interaction effects for overweight showed patterns consistent with the effects for obesity, but none of the interactions reached statistical significance.

Our study showed that female sex interacted synergistically with obesity leading to greater than additive increases in the rate of accumulation of MM. These results are in agreement with a previous cross-sectional study showing that Brazilian women with obesity had a greater than expected odds of MM.[13] However, we found that women had a higher rate of MM accumulation compared to men only in the 20- and 40-year age cohorts, whereas men had a higher rate of MM accumulation in the 60- and 80-year age cohorts. Similarly, female sex interacted significantly with obesity in the 20- and 40-year age cohorts, but not the 60- and 80-year

Table 2. Multivariable model of association between characteristics and the rate of accumulation of multi-morbidity (per 10 years).

	20-year-old cohort		40-year-old cohort		60-year-old cohort		80-year-old cohort	
	MM accumulation	Adjusted †	MM accumulation	Adjusted †	MM accumulation	Adjusted †	MM accumulation	Adjusted †
Characteristic	rate (95% CI)*	RR (95% CI)	rate (95% CI)*	RR (95% CI)	rate (95% CI)*	RR (95% CI)	rate (95% CI)*	RR (95% CI)
BMI category								
Normal	0.53 (0.51, 0.55)	1 (reference)	0.86 (0.82, 0.89)	1 (reference)	2.31 (2.24, 2.37)	1 (reference)	4.67 (4.52, 4.82)	1 (reference)
Overweight	0.64 (0.60, 0.67)	1.18 (1.12, 1.25)	1.15 (1.12, 1.19)	1.31 (1.26, 1.36)	2.47 (2.41, 2.52)	1.05 (1.01, 1.08)	4.91 (4.80, 5.03)	1.03 (0.99, 1.07)
Obese	0.93 (0.88, 0.98)	1.64 (1.57, 1.70)	1.84 (1.80, 1.89)	2.05 (2.01, 2.10)	3.12 (3.06, 3.17)	1.31 (1.28, 1.35)	5.55 (5.41, 5.70)	1.16 (1.12, 1.20)
Sex								
Women	0.67 (0.65, 0.70)	1 (reference)	1.26 (1.23, 1.29)	1 (reference)	2.57 (2.53, 2.61)	1 (reference)	4.85 (4.74, 4.95)	1 (reference)
Men	0.54 (0.51, 0.56)	0.79 (0.73, 0.84)	1.35 (1.31, 1.38)	0.97 (0.93, 1.00)	2.86 (2.81, 2.91)	1.06 (1.04, 1.09)	5.33 (5.21, 5.45)	1.06 (1.02, 1.09)
Race								
White	0.61 (0.59, 0.62)	1 (reference)	1.29 (1.27, 1.31)	1 (reference)	2.69 (2.65, 2.72)	1 (reference)	5.06 (4.99, 5.14)	1 (reference)
Black	0.78 (0.70, 0.86)	1.23 (1.13, 1.34)	1.61 (1.48, 1.73)	1.12 (1.04, 1.20)	3.22 (2.93, 3.52)	1.20 (1.11, 1.29)	4.42 (3.68, 5.15)	0.85 (0.68, 1.02)
Asian	0.47 (0.40, 0.54	0.79 (0.63, 0.95)	1.07 (0.98, 1.16)	1.05 (0.96, 1.13)	2.80 (2.61, 3.00)	1.15 (1.08, 1.22)	4.83 (4.25, 5.40)	0.98 (0.86, 1.10)
Other/mixed	0.71 (0.62, 0.79)	0.99 (0.86, 1.12)	1.51 (1.39, 1.63)	1.15 (1.06, 1.24)	3.21 (2.96, 3.47)	1.22 (1.14, 1.31)	5.18 (4.53, 5.82)	1.01 (0.88, 1.14)
Unknown	0.14 (0.05, 0.23)	0.29 (-0.35, 0.94)	0.82 (0.59, 1.06)	0.70 (0.41, 0.99)	2.12 (1.70, 2.54)	0.85 (0.65, 1.05)	3.54 (1.55, 5.53)	0.68 (0.12, 1.24)
Ethnicity								
Non-Hispanic	0.60 (0.59, 0.62)	1 (reference)	1.30 (1.28, 1.32)	1 (reference)	2.71 (2.67, 2.74)	1 (reference)	5.05 (4.98, 5.13)	1 (reference)
Hispanic	0.73 (0.65, 0.80)	1.13 (1.00, 1.25)	1.26 (1.17, 1.36	0.87 (0.78, 0.95)	2.66 (2.47, 2.85)	0.91 (0.83, 0.98)	5.05 (4.39, 5.72)	0.97 (0.83, 1.10)
Education level								
>High school	0.79 (0.75, 0.83)	1 (reference)	1.82 (1.74, 1.89)	1 (reference)	3.18 (3.10, 3.26)	1 (reference)	5.44 (5.32, 5.57)	1 (reference)
≤High School	0.62 (0.60, 0.64)	1.12 (1.06, 1.18)	1.27 (1.25, 1.30)	1.26 (1.21, 1.30)	2.67 (2.63, 2.70)	1.13 (1.10, 1.16)	4.82 (4.71, 4.92)	1.12 (1.09, 1.15)
Unknown	0.39 (0.36, 0.42)	0.58 (0.50, 0.67)	0.88 (0.82, 0.94)	0.63 (0.56, 0.71)	1.68 (1.57, 1.78)	0.60 (0.53, 0.67)	3.17 (2.77, 3.56)	0.65 (0.52, 0.79)
Smoking status								
Never	0.41 (0.39, 0.43)	1 (reference)	1.04 (1.00, 1.07)	1 (reference)	2.31 (2.25, 2.36)	1 (reference)	4.48 (4.35, 4.60)	1 (reference)
Former/current	0.99 (0.94, 1.03)	2.26 (2.19, 2.33)	1.68 (1.64, 1.73)	1.51 (1.47, 1.54)	3.06 (3.01, 3.11)	1.29 (1.26, 1.32)	5.44 (5.33, 5.55)	1.19 (1.16, 1.23)
Unknown	0.64 (0.62, 0.67)	1.75 (1.69, 1.82)	1.21 (1.16, 1.25)	1.30 (1.24, 1.35)	2.53 (2.45, 2.61)	1.22 (1.18, 1.26)	4.96 (4.74, 5.19)	1.15 (1.09, 1.20)

BMI = body mass index; CI = confidence interval; MM = multi-morbidity; RR = relative risk.

*The multi-morbidity incidence rates are reported per 10 person-years.

†Risk ratios in each age cohort column come from a single full multivariable model including all variables shown in the table.

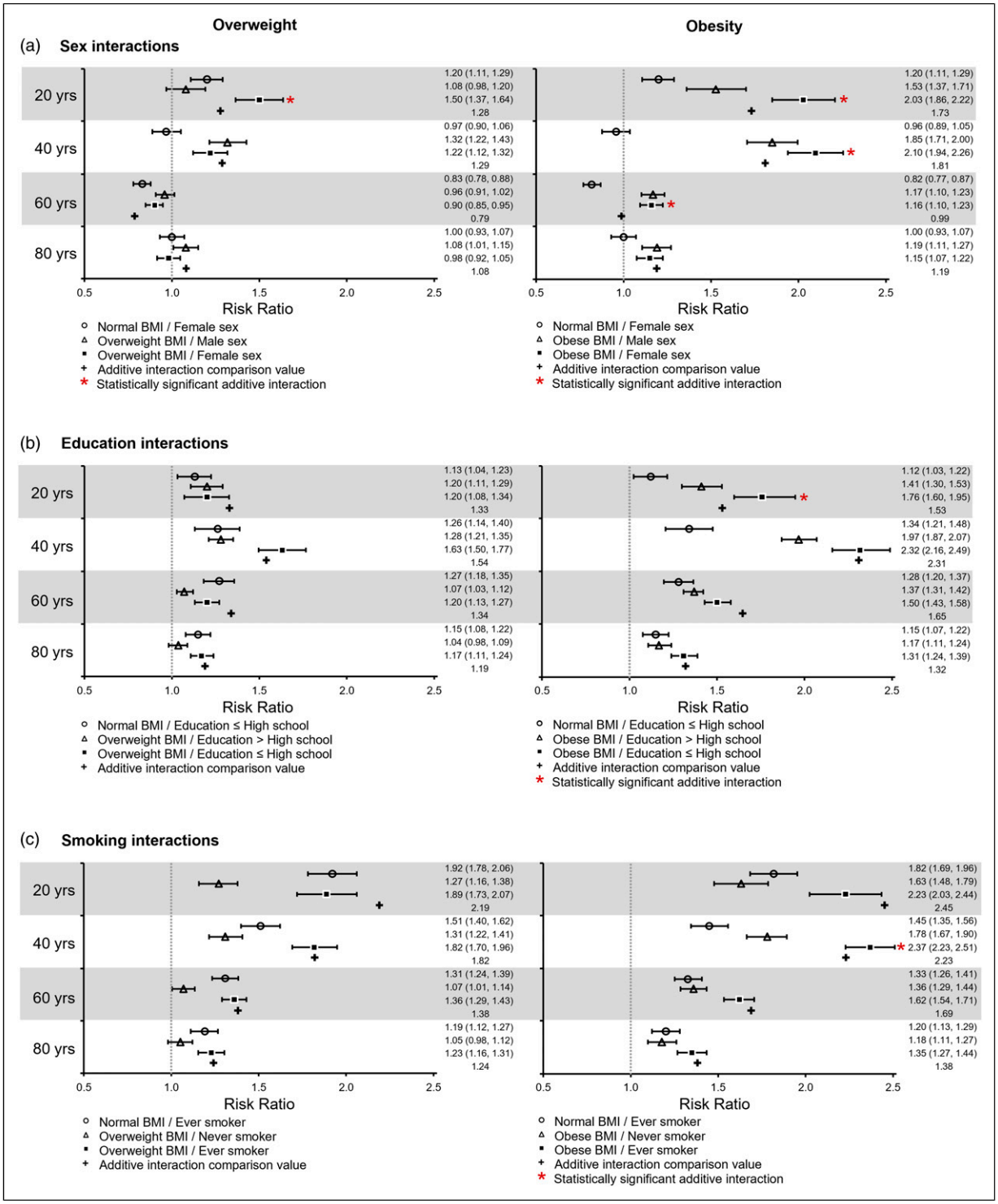

Figure 2. 2A displays interactions between overweight (left) or obesity (right) and sex. The referent population was persons of normal weight and male sex. 2B displays interactions between overweight or obesity and education. The referent population was persons of normal weight and greater than high school education. 2C displays interactions between overweight or obesity and smoking. The referent population was persons of normal weight and never smokers.

cohorts. These data suggest that the impact of sex on accumulation of MM changes over the lifespan, and that interventions targeting women living with obesity may need to occur prior to midlife to have the greatest effect in reducing rate of MM accumulation.

Our results showing synergistic additive interactions between lower education level or smoking status and obesity on the rate of MM accumulation are novel. However, our results are consistent with a previous study in which smoking and obesity interacted to increase the odds of self-reported cardiovascular disease more than the independent effects of these variables alone.[10] Cardiovascular disease is only one component of our definition of MM, and our results suggest that persons who had lower education or were former or current smokers and had obesity are also at especially high risk of rapidly accumulating other chronic conditions. In addition, like the sex and obesity interactions, interactions between education and obesity were statistically significant only in the 20-year age cohort, and interactions between smoking and obesity were only significant in the 40-year age cohort. These results suggest that timing of interventions in persons with these characteristics may be important, and interventions prior to middle age may have a greater impact on reducing the rate of MM accumulation.

Finally, we found that persons of Black race, Asian race, or Hispanic ethnicity were at an increased risk of accumulating MM compared to persons of White race or non-Hispanic ethnicity; however, the impact of race and ethnicity differed across the age cohorts. Black race was consistently associated with an increased risk of MM accumulation in the 20, 40, and 60 year age cohorts, whereas associations between Asian race or Hispanic ethnicity and MM accumulation varied at different ages. We also found that race and ethnicity did not interact with obesity to increase the risk of MM accumulation at greater than additive levels in any of the age groups. Therefore, our data are consistent with a previous study that did not show significant interactions between Black race, Hispanic ethnicity, and obesity on risk of MM accumulation.[7] Together, these data suggest that the effects of race and ethnicity vary across the lifespan, and that minority race and ethnicity and obesity are independent risk factors for increased rate of MM accumulation (no interactions).

Our study has a number of strengths. First, most previous MM studies focused only on middle-aged or older-aged populations, and data on the development and progression of MM are limited in younger populations. However, interventions to delay or prevent the progression of MM may need to occur earlier in life before MM is well-established. Therefore, it is important to understand the onset and progression of MM over the life-course to understand when interventions may have an optimal impact. To address these gaps, we studied 4 separate age cohorts, representing young, middle-aged, older, and elderly populations. Age is strongly associated with MM, and our study design allowed us to remove the effect of age from the analyses focused on interactions between BMI and other variables, while still allowing us to study the effect of interactions with BMI across the life-course. Our results suggest that some characteristics (sex, race, and ethnicity) may have a different impact on MM accumulation at different ages. Second, studies examining interactions are relatively uncommon partly because such studies require large sample sizes to identify subpopulations at especially high risk. Our study focused on 4 large age-specific cohorts, allowing for more precise estimates of risk and for the ability to detect interactions.

Limitations of our study include the use of ICD codes to identify the chronic conditions included in our definition of MM. The sensitivity and specificity of these codes are different across conditions, and some conditions may be missed, particularly in younger persons who visit a health care provider less frequently.[19] The REP includes data from the main sources of health care in the region, but does not include data from private optometrists and mental health providers (e.g., local private psychotherapists). In addition, some persons may have received chronic condition diagnoses from health care providers who do not participate in the REP (e.g., Veterans Administration). Similarly, our results rely on capture of chronic conditions from medical records, and health care providers may not completely document the presence of all chronic conditions. Finally, 2 diagnostic codes separated by more than 30 days were required to identify the presence of a chronic condition. Each of these circumstances may have reduced our ability to completely identify all chronic conditions in our study cohorts. However, incomplete data for the chronic conditions could result in a lower rate of accumulation of chronic conditions, and our results would be biased toward no association. Thus, our results are likely to be conservative.

We were also limited to use of BMI as a surrogate measure for obesity, because other, more precise measures of obesity (e.g., waist to hip ratio) are not routinely assessed during the course of clinical care. BMI measures may overestimate obesity in younger persons with substantial muscle and may underestimate obesity in older persons who have lost muscle mass. We expect misclassification in both older and younger persons to bias our results toward no association. Improved fitness is associated with a decreased risk in MM, and our results in younger persons may be conservative. By contrast, we may have been unable to detect associations in older persons. This study also focused on persons residing in the upper midwest. Sociodemographic characteristics differ throughout the country, and populations at highest risk of MM accumulation may differ in other regions.

We also note that the number of years persons have lived with their conditions, the severity of the conditions, and the types of treatments received for the conditions are likely to have a significant effect on the rate of accumulation of MM.

BMI may interact with other patient characteristics to influence the rate of accumulation of MM in different ways depending on the severity, duration, and types of treatment received for the individual conditions. Unfortunately, determining duration of illness and severity of disease from medical record information is difficult, and it was not possible to assess the impact of duration, severity, and treatment on our study results. Such studies should be pursued in the future to better understand the populations at highest risk of rapid MM accumulation. Finally, we have previously reported the most common conditions included in incident and prevalent MM in the Olmsted County population.[22, 23] BMI may have a differential effect on the rate of accumulation of different MM conditions. Such analyses were also beyond the scope of this study, but would build on the results of this study, and represent important areas for future investigation.

In conclusion, we found that female sex, lower education, and former or current smoking status interacted synergistically with obesity to increase the risk of accumulating MM more rapidly than would be expected just by adding the individual effects together. These data suggest that interventions targeted at women, persons with lower education, and former or current smokers who have obesity may result in the greatest reduction in the rate of MM accumulation. However, statistically significant interactions were primarily observed in the 20- and 40-year age cohorts. Therefore, such interventions may need to be focused on persons prior to midlife to have the greatest preventive effect.

Acknowledgement

We thank Trisha Shulze for assistance with formatting and submitting this manuscript.

Author contributions

Conceptualization: JLS, BRG, WAR; Methodology: BRG, AMC; Formal Analysis: JLS, BRG, WAR; Writing-original draft: JLS, BRG, WAR; Writing-review and editing: JLS, BRG, WAR, AMC, EK; Supervision: JLS, WAR; Project administration: BRG, AMC; Funding acquisition: JLS, WAR; Guarantor for the overall content: JLS, BRG.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institute on Aging (R01 AG 052425 and R33 AG 058738). In addition, this study used the resources of the Rochester Epidemiology Project (REP) medical records-linkage system, which is supported by the Mayo Clinic Research Committee and by fees paid annually by REP users. The content of this article is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health (NIH) or the Mayo Clinic.

ORCID iDs

Jennifer L. St Sauver https://orcid.org/0000-0002-9789-8544
Alanna M Chamberlain https://orcid.org/0000-0003-1888-9584
Walter A Rocca https://orcid.org/0000-0002-1832-7664

Supplemental Material

Supplemental material for this article is available online.

References

1. Fabbri E, Zoli M, Gonzalez-Freire M, et al. Aging and multimorbidity: new tasks, priorities, and frontiers for integrated gerontological and clinical research. *J Am Med Dir Assoc*. 2015;16(8):640-647.
2. Calderon-Larranaga A, Santoni G, Wang HX, et al. Rapidly developing multimorbidity and disability in older adults: does social background matter? *J Intern Med*. 2018;283(5):489-499.
3. Agborsangaya CB, Ngwakongnwi E, Lahtinen M, et al. Multimorbidity prevalence in the general population: the role of obesity in chronic disease clustering. *BMC Public Health*. 2013;13:1161.
4. Canizares M, Hogg-Johnson S, Gignac MAM, et al. Increasing Trajectories of Multimorbidity Over Time: Birth Cohort Differences and the Role of Changes in Obesity and Income. *J Gerontol B Psychol Sci Soc Sci*. 2018;73(7):1303-1314.
5. Kivimaki M, Kuosma E, Ferrie JE, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. *Lancet Public Health*. 2017;2(6):e277-e285.
6. Mounce LTA, Campbell JL, Henley WE, et al. Predicting incident multimorbidity. *Ann Fam Med*. 2018;16(4):322-329.
7. Botoseneanu A, Markwardt S, Nagel CL, et al. Multimorbidity Accumulation Among Middle-Aged Americans: Differences by Race/Ethnicity and Body Mass Index. *J Gerontol A Biol Sci Med Sci*. 2022;77(2):e89-e97.
8. VanderWeele TJ and Tchetgen Tchetgen EJ. Attributing effects to interactions. *Epidemiology*. 2014;25(5):711-722.
9. Rothman KJ, Greenland S and Walker AM. Concepts of interaction. *Am J Epidemiol*. 1980;112(4):467-470.
10. Luo WS, Chen F, Ji JM and Guo ZR. Interaction of tobacco smoking and alcohol consumption with obesity on cardiovascular disease in a Chinese cohort. *Coron Artery Dis*. 2020;31(4):372-377.
11. Luo W, Guo Z, Wu M, et al. Interaction of smoking and obesity on type 2 diabetes risk in a Chinese cohort. *Physiol Behav*. 2015;139:240-243.
12. Mozafar Saadati H, Sabour S, Mansournia MA, et al. Effect modification of general and central obesity by sex and age on cardiovascular outcomes: Targeted maximum likelihood estimation in the atherosclerosis risk in communities study. *Diabetes Metab Syndr*. 2021;15(2):479-485.

13. Flores TR, Rodrigues APDS, Neves RG, et al. The Risk of Multimorbidity Associated with Overweight and Obesity: Data from the Brazilian National Health Survey 2013. *J Obes Metab Syndr*. 2021;30(2):155-162.
14. St Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *Int J Epidemiol*. 2012;41(6):1614-1624.
15. St Sauver JL, Grossardt BR, Yawn BP, et al. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester Epidemiology Project. *Am J Epidemiol*. 2011;173(9):1059-1068.
16. Rocca WA, Grossardt BR, Brue SM, et al. Data resource profile: Expansion of the Rochester Epidemiology Project medical records-linkage system (E-REP). *Int J Epidemiol*. 2018;47(2):368.
17. Flegal KM, Graubard BI, Williamson DF, et al. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2007;298(17):2028-2037.
18. Goodman RA, Posner SF, Huang ES, et al. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis*. 2013;10: E66.
19. St Sauver JL, Chamberlain AM, Bobo WV, et al. Implementing the US Department of Health and Human Services definition of multimorbidity: a comparison between billing codes and medical record review in a population-based sample of persons 40-84 years old. *BMJ Open*. 2021;11(4):e042870.
20. Porta M. A Dictionary of Epidemiology. In: Porta M, editor. *A Dictionary of Epidemiology*. Sixth Edition ed. New York, NY: Oxford University Press; 2014. p. 239.
21. Lundberg M, Fredlund P, Hallqvist J, et al. A SAS program calculating three measures of interaction with confidence intervals. *Epidemiology*. 1996;7(6):655-656.
22. Rocca WA, Boyd CM, Grossardt BR, et al. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. *Mayo Clin Proc*. 2014;89(10):1336-1349.
23. St Sauver JL, Boyd CM, Grossardt BR, et al. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open*. 2015;5(2):e006413.