

Original Research Article

Title: The Association Between Weight Loss Medications and Cardiovascular Complications

Short Title: New Obesity Drugs and CVD

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What is already known?

- Obesity is an important modifiable risk factor for cardiovascular disease (CVD).
- Newly approved anti-obesity medications (AOM) have been shown to be an effective way to manage obesity.

What is new?

- Original research using real world data that investigates the effect of newly approved AOM on several cardiovascular diseases.
- Our study showed an 8% relative risk reduction in any CVD events.

How might your results change the direction of research or the focus of clinical practice?

- AOM utilization among people with obesity, a modifiable risk factor, could potentially alleviate the high prevalence of CVD.
- AOM use in patients with obesity was associated with less incidence of heart failure and atrial fibrillation compared to patients with obesity without AOMs.

ABSTRACT

Objective: Obesity and its cardiovascular complications are major causes of morbidity and mortality. Little is known in real-world settings about the effect of newly approved anti-obesity medications (AOMs) on cardiovascular complications among patients with obesity.

Methods: This retrospective cohort study examined the association between newly approved AOM use and cardiovascular events among Medicare patients with obesity using data from 2020 to 2022. Patients age, gender, comorbidities scores, SES, and baseline cardiovascular comorbidities are compared descriptively. Subgroup analysis compared variables by medication type. Relative risk and absolute risk of CVD events was estimated using Cox, and Aalen's regression model.

Results: 5,926 patients were treated with AOM, including Ozempic (5,404 patients), Wegovy (375 patients), or Mounjaro (147 patients). Hypertension, type 2 diabetes, and hyperlipidemia were the most common comorbidities. For patients with AOM, less incidence of heart failure (4.89% vs 6.13%, $p<.0001$), atrial fibrillation (3.83% vs 5.17%, $p<.0001$), arrhythmia (3.59% vs 4.14%, $p<.0153$) and peripheral vascular disease (3.44% vs 2.94%, $p<.0395$) was found vs patients without AOM. Patients receiving AOMs showed 8% risk reduction in any CVD. Protective effect on CVD was apparent over the first 375 days.

Conclusions: Results suggest that utilization of AOMs effectively alleviates the high prevalence of CVD.

Keywords: obesity, anti-obesity medications, semaglutide, tirzepatide, Ozempic, Wegovy, cardiovascular disease, cardiovascular risk factors

Introduction

Obesity is an important modifiable risk factor for cardiovascular disease (CVD). Newly approved anti-obesity medications have been shown to be an effective way to manage obesity. They not only improve weight loss but also reduce the risk of obesity-related complications.¹ Recent clinical data suggest that AOMs can positively impact cardiovascular events in individuals with overweight and obesity.² The precedent-setting results with semaglutide and tirzepatide, which have shown a mean weight loss of over 10% and have been proven to improve cardiovascular outcomes in type 2 diabetes, inspire confidence for the future.³

Glucagon-like peptide 1 (GLP-1) based medications such as semaglutide and tirzepatide were first approved only for improved glucose control.⁴ Common side effects of these medications, which include weight loss, better glucose control, or a combination of the two, may contribute to the reduced risk of CVD associated with these medications.⁴

Ozempic was approved in 2017 as a diabetic treatment found to cause weight loss of up to 15% of body weight.⁵ This weight loss effect led to the development of Wegovy, a drug with a higher maximum dose, which the FDA approved for long-term weight management in 2021.⁶ Tirzepatide was undergoing an FDA fast-track investigation for the treatment of adults with overweight or obesity and weight-related comorbidities.⁷ Clinical trials had shown promising results with participants losing around 20% or more of their body weight within a year and a half of starting the treatment.⁵ In November 2023, the FDA approved tirzepatide for weight loss under the brand name Zepbound.⁸

Among Medicare beneficiaries aged 65 years and over, almost 50% have at least one heart condition and those with at least one heart conditions had, on average, almost double the total cost of care compared with those without heart conditions.⁹

Although health economists have warned that the costs of expanding Medicare prescription drug coverage to pay for expensive new AOMs could be catastrophic, Medicare's decades-old exclusion of weight loss drug coverage is coming under scrutiny amid mounting evidence that AOMs have health benefits that extend well beyond shedding pounds.

Yet, there is limited research using real-world data to explore the association between AOMs and their association with costly CVDs. To address this gap, we conducted a retrospective cohort study to analyze the impact of approved obesity medications, such as Ozempic, Wegovy, and Mounjaro, on CVD. We hypothesize that AOMs would have a protective effect on the risk of cardiovascular disease.

Methods

We utilized Kythera Medicare claims data from January 2020 to August 2022, employing a retrospective cohort design. The data contains medical and pharmacy claims and commercial, Medicaid, and Medicare fee-for-service and managed-care patients.¹⁰ The data includes both open and closed versions, covering approximately 310 million patients, 6.1 million practitioners, 1.6 million organizations, and 1.4 million facilities, generating 34 billion healthcare claims.^{10,11} The data include the unique de-identified numbers of patients, age, gender, type of insurance, zip codes, diagnosis according to the *International Classification of Diseases, Tenth Revision* (ICD-10), CPT codes, and NDCs for medications, allowing for longitudinal analysis. The details of the data have been published elsewhere and compared with other data sets for their validity and consistency.^{10,11}

We identified two cohorts of patients with obesity: patients treated with AOMs and those not treated with AOM (non-AOM) (medication ICD Codes can be found in Table S1). For the AOM cohort, we identified patients who had one or more pharmacy claims for Ozempic,

Wegovy, or Mounjaro between January 1, 2021, and August 31, 2022 (identification period). During this time period, Wegovy was the only medication FDA-approved for weight loss, however Ozempic and Mounjaro were included in the AOM cohort since they have also been shown to cause significant weight loss.^{5,7} The first prescription claim was considered the treatment initiation date and index date for the AOM group. The patients in the AOM group had at least one claim with a diagnosis of obesity (ICD-10 CM: E66.9, E66.09, E66.1, E66.8, and Z68.3; Table S3) prior to the index date and had continuous medical and pharmacy benefits for 12 months before and 12 months after the index date.

For the non-AOM cohort, we identified patients with at least one claim with an obesity diagnosis during the baseline period (January 1, 2020–January 1, 2021). The index date for this group was selected at random between a minimum date of index medication from the AOM group and a maximum date of index medication from the AOM group. The same continuous enrollment requirement applied to the non-AOM cohort. Patients prescribed any obesity medication during the baseline, those with more than one claim of obesity medication on the same index date, those with any CVD during the baseline, and those aged 99 years and older were excluded from the study. After applying inclusion and exclusion criteria for the non-AOM group, 10% of patients in this cohort were chosen randomly to be included in the final sample.

Figure 1 illustrates the study period and inclusion and exclusion criteria.

We analyzed numerous clinical and demographic aspects at their baseline. Kythera Medicare claims data included gender (male or female) and age (65-70, 71-80, or >80 years). We utilized income, education, and occupation information from the 5-year estimates for the 2021 U.S. Census data to evaluate a previously established summary measure of socioeconomic status (SES) for each U.S. zip code.¹² Based on their summary SES scores, the subjects were

categorized into terciles (low, medium, and high).¹² To accommodate differences in total comorbidities among patients, we developed three comorbidity indices: the revised Charlson Comorbidity Index (CCI)¹³, the Chronic Disease Score (CDS)¹³, and the Elixhauser Index.¹⁴

Using the appropriate ICD-10 codes (Table S2), we then proceeded to define the likelihood of CVD as the presence of coronary artery disease, heart failure, atrial fibrillation, arrhythmia, ischemic heart disease, stroke, and peripheral vascular disease.

Descriptive analysis conducted for the AOM and non-AOM cohorts, and a subgroup analysis was performed by comparing the variables by medication type. To compare the risk of CVD between the groups, we utilized Cox regression and Aalen's additive regression models. For Cox regression and Aalen's additive regression model, we controlled for the following cofounders as age, gender, comorbidities scores, SES score and obesity-related comorbidities. Aalen's model is applied to see if the effect of treatment is additive (i.e., changes over time). For example, while the effect of a treatment on the development of CVD may not be significant in the Cox analysis, an additive model can reveal a significant effect in the first year, with the effect diminishing in subsequent years.¹⁵

Likelihood ratio tests were used to compare differences between two groups, while Wald tests were employed to compare differences between three or more groups. We conducted all analyses on Databricks using Pyspark, SparkR, and the R software package.

Ethics approvals for this study were not required as the data utilized were from an anonymous, de-identified database compliant with HIPAA. This study was performed in accordance with the Declaration of Helsinki.

Results

After applying inclusion and exclusion criteria, 5,926 patients were identified in the AOM cohort and 79,118 patients in the non-AOM cohort (attrition tables can be found in Table S4 and S5).

Average patient age in the AOM cohort was lower than in the non-AOM cohort (71.53 vs. 73.67, $p<.0001$). For both groups, most patients were female (64.07% vs. 61.15%, $p<.0001$). High-comorbidity patients were defined as those with a comorbidity score of 2 and above. The AOM cohort had a significantly higher proportion of patients with a high CCI (50.10% vs. 25.29%, $p<.0001$), high CDS (81.00% vs. 37.43%, $p<.0001$), and high Elixhauser Index (90.58% vs. 68.69%, $p<.0001$). The AOM cohort also had a higher proportion of individuals living in low-SES regions (34.35% vs. 32.93%, $p=.0262$).

All baseline CVD-related comorbidities were higher in the AOM group, including the three most prevalent in both cohorts: hypertension (72.44% vs. 61.07%, $p<.0001$), type 2 diabetes (64.83% vs. 25.44%, $p<.0001$), and hyperlipidemia (39.08% vs. 30.42%, $p<.0001$), followed by smoking history (7.42% vs. 6.31%, $p=.0007$), chronic obstructive pulmonary disease (COPD) (6.83% vs. 6.19%, $p=.0468$), and chronic kidney disease (3.29% vs. 2.26%, $p<.0001$). The prevalence of alcohol use disorder was not statistically significantly different between the two cohorts (**Table 1**).

The unadjusted analysis showed that the proportion of any CVD outcomes was significantly lower in the AOM cohort versus the non-AOM cohort (19.36% vs. 21.16%, $p=.0010$). Moreover, the proportion of the majority of the analyzed CVDs, including heart failure (4.89% vs. 6.13%, $p=.0001$), atrial fibrillation (3.83% vs. 5.17%, $p<.0001$), arrhythmia (3.49% vs. 4.14%, $p=.0153$), and peripheral vascular disease (2.94% vs. 3.44%, $p=.0395$) was significantly lower in the AOM cohort versus the non-AOM cohort; only ischemic heart disease

was higher in the AOM cohort (0.34% vs. 0.20%, $p=.0289$). Coronary artery disease and stroke were not significantly different between the two cohorts (**Table 2**).

Table 3 shows Cox regression results for the risk of CVD in the AOM and non-AOM cohorts. AOM usage among patients with obesity was associated with an 8% reduction in the risk of CVD compared with those who did not use AOM (HR=0.92, $p=.0068$, 95% CI: 0.86-0.98). Patients in the 71-80 years age group (HR: 0.67, $p<.0001$, 95% CI: 0.64-0.70) had a 33% reduced risk of CVD compared to the 65-70 years patient age group. However, patients in the 80+ age group (HR:2.01, $p<.0001$, 95% CI: 1.92-2.10) had a 2.01 times greater risk compared to patients in the 65-70 years age group.

Females had a 26% reduced risk of CVD compared with males (HR: 0.74, $p<.0001$, 95% CI: 0.72-0.77). Individuals in low- (HR: 1.09, $p<.0001$, 95% CI: 1.05-1.13) and medium- (HR: 1.07, 95% CI: 1.03-1.11) SES regions had a 9% and 7% increased risk of CVD, respectively, compared with high-SES regions. CCI ≥ 2 (HR: 1.40, $p<.0001$, 95% CI: 1.34-1.45), CDS ≥ 2 (HR: 1.12, $p<.0001$, 95% CI: 1.08-1.15), COPD (HR: 1.41, $p<.0001$, 95% CI: 1.33-1.48), smoking history (HR: 1.12, $p=.000$, 95% CI: 1.06-1.19), and chronic kidney disease (HR: 1.17, $p=.0005$, 95% CI: 1.07-1.27) were associated with an increased risk of CVD.

Figure 2 describes the results of Aalen's additive regression. The analysis shows that AOM treatment had a protective effect on CVD over approximately the first 375 days. After that, the treatment did not significantly affect the CVD outcomes. Being younger and female had a protective effect on CVD over the entire period of 1000 analyzed days. On the other hand, a sustained increased risk of CVD could be seen among patients with high CCI and CDS, those living in areas with low and medium SES scores, and those with COPD. Hyperlipidemia had a protective effect against CVD in the first 120 days and between 760 and 920 days; however, the

disease increased the risk of having CVD after approximately 920 days. Smoking history increased the risk of CVD in the first 660 days and chronic kidney disease increased the risk of CVD during approximately the first 700 days.

Discussion

Obesity is a significant risk factor for CVD, and most obesity-related deaths are due to CVD.^{16,17} Additionally, a wealth of evidence demonstrating this association has shown that losing weight is an effective method for preventing CVD.^{3,18} A decrease in body weight of 5% to 10% can provide a clinically meaningful improvement in glycated hemoglobin levels, blood pressure, and cholesterol levels, and these cardiometabolic improvements are progressively enhanced with further weight loss.^{3,19} Therefore, AOMs have revolutionized treatment for weight loss as they have shown significant weight loss and overall improvement in CVD. However, to our knowledge, there are no studies investigating the relationship between AOMs and CVD using real-world data. Therefore, this study provides significant insights on how AOM has an effect on the incidence of CVD in individuals with obesity.

Our results indicated that AOM usage was correlated with an 8% reduced risk of CVD compared with those who did not utilize AOM. Our results showed that individuals in the AOM cohort were slightly younger (72 vs. 74 years), had a higher proportion of females (64.70%), and had a higher proportion of individuals living in low-SES regions (34.35%). Furthermore, the individuals in the AOM cohort were sicker, which was expected since medications such as Ozempic and Mounjaro are indicated for patients with weight-related comorbidities, including diabetes or hyperlipidemia, in addition to obesity.^{7,20,21}

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In this study of patients with obesity, the CVD-related comorbidities with the highest prevalence were hypertension (72.44%), type 2 diabetes (64.83%), and hyperlipidemia (39.08%). Those in the AOM cohort prior to medication were 19% more likely to have hyperlipidemia, 155% more likely to have type 2 diabetes, and 28% more likely to have hyperlipidemia than individuals in the non-AOM group. Consequently, living in a low-SES region and having COPD, smoking history, chronic kidney disease, and increased CCI and CDS scores were correlated with an elevated risk of CVD for all individuals in the study. These results are consistent with literature stating that low-SES individuals tend to be more affected by CVD than those of higher SES.²² Our results are also consistent with literature suggesting that patients with more comorbidities are at a greater risk of developing CVD.²³

Although individuals in the AOM cohort were sicker, the unadjusted analysis demonstrated that the percentage of any CVD outcome was significantly lower in the AOM cohort than in the non-AOM cohort (approximately 9%). Individuals in the AOM cohort demonstrated a reduction in the incidence of heart failure by 25%, atrial fibrillation by 35%, arrhythmia by 18.6%, and peripheral vascular disease by 17%. Our study showed a reduction in the incidence of heart failure, which supports the findings of previous studies that have demonstrated AOM's effectiveness in improving health outcomes of patients with heart failure.²⁴ The STEP-HF trial, released in August, reported that pharmacotherapy improved heart failure with preserved Ejection Fraction among adults with obesity.²⁵ Furthermore, these findings correlated with findings from the SELECT Topline trial that reported that 2.4 mg semaglutide reduced the risk of major adverse cardiovascular events by 20% in adults with overweight or obesity.^{26,27} Moreover, our results are consistent with previous studies that state heart failure and atrial fibrillation have become among the most prevalent heart conditions in recent years.^{28,29}

After adjusting for confounding variables, such as clinical and sociodemographic variables, between the cohorts, our study indicated an 8% reduction in the risk of CVD. In addition, our analysis showed that AOM treatment had a protective effect against CVD over approximately the first 375 days. After that time, the treatment did not significantly affect the CVD outcomes. Patients aged 71-80 years old and females had a reduced risk of CVD. However, patients aged 80 years old or older had a 2.01 times greater risk of CVD. This is consistent with the American Heart Association that has reported the incidence of CVD in US men and women increases with age especially above the age of 80^{30,31}.

Individuals in low and medium SES regions had a 9% and 7% increase in the risk of CVD, respectively. A higher comorbidity score, indicating that a patient is sicker (as patients with a higher score have more comorbidities or more medications), was associated with a higher risk of CVD. Individuals with COPD had a 41% increased risk of CVD, smoking history had a 12% increased risk of CVD, and chronic kidney disease had a 17% increased risk of CVD. This is consistent with significant literature that have addresses how smoking, COPD and chronic kidney disease are risk factors for CVD^{32,33}.

It should be noted that hyperlipidemia (HR: 0.95, $p=.0012$, 95% CI: 0.91-0.98) was associated with a 5% decreased risk of CVD. This finding is inconsistent with previous literature.³⁴ We believe the possible reason for this finding is that these patients are being treated for hyperlipidemia, a major risk factor for CVD, therefore treating hyperlipidemia would be accounted as a well-known protective effect^{35,36}. This finding should be interpreted with caution and further studies should be done regarding the cumulative effect of using AOMs and treatment for other baseline comorbidities.

No significant differences in CVD were observed between those treated with Ozempic versus Wegovy versus Mounjaro.

The reduced risk and lower incidence of CVD outcomes demonstrated in this study indicate that AOM treatment could be an effective solution for alleviating the high prevalence of CVD. According to the CDC, in the U.S., CVD claims one life every 33 seconds.²⁹ The World Health Organization reported in 2019 that CVD accounted for 17.9 million deaths globally, making it the world's leading cause of mortality.³⁶ Additionally, in 2019, noncommunicable illnesses accounted for 17 million premature fatalities (deaths of individuals <70 years of age) of which 38% were attributed to CVD.³⁶ By 2035, CVD is projected to affect approximately 50% of American adults.³⁷ The amount of CVD spending by Americans has rapidly increased in previous years. One study noted that between 1996 and 2016, spending on CVD elevated from \$212 billion to \$320 billion.³⁷ Adding to the economic burden, the U.S. spends \$190 billion annually for obesity-related illnesses such as CVD.^{3,38} Obesity and CVD are so interconnected that improving cardiovascular health constitutes a primary objective for weight loss therapies.³

Limitations

This study has several limitations related to the use of administrative data sets, which may be subject to inaccurate coding of patient clinical diagnoses and procedures, as well as clinical information limited to conditions and treatments defined by ICD-10-CM codes. Since the analysis was done on the review of claims data that were not originally designed for research, some information will be missing. First, as with most claims-based data sources, there is a time lag between an individual's receipt of services and when the files become available for research (average, 2-3 years). The data may not be generalizable to the entire population, as some information may be missed in processing or reimbursement. Additionally, not all health data are

captured in the claims. Medicare claims data has the limitation that information on body size or BMI is not captured, and we recognized this information is essential for obesity-related medications. Furthermore, patients with obesity identified through ICD-10 codes can result in underestimation of the cases. A recent study showed 75% of patients with obesity are underdiagnosed.³⁹ Therefore, to the extent that differences in CV risk systematically differ for the undiagnosed cases our estimates can be biased.

Furthermore, in our study we did not address adherence to medication, and recognized this can be a limitation to our results. Moreover, we recognized our study has the limitation that patients with certain comorbidities such as hyperlipidemia or diabetes might be receiving proper treatment for these baseline conditions which will have a protective effect on the incidence of cardiovascular disease. As we mentioned before, we encourage further studies that control for the effect these medications plus AOM might have in the incidence of cardiovascular disease.

The utilization of area-based measurements presents another possible limitation of our study. Since employing area-based measures alone unavoidably misclassifies persons within areas on both ends of the socioeconomic spectrum, it would have been ideal if we could have evaluated both individual and area-based socioeconomic metrics. The bias's direction is known, while the misclassification is random.⁴⁰ If there is a difference in SES between areas, it is likely to be more pronounced when individual SES is taken into account. An advantage of area-based measurements is their capacity to include contextual data about many aspects that affect every person in a given region, such as the location and quality of public facilities like hospitals.⁴¹ Since zip codes were created to form socioeconomically comparable groupings, our estimates would also be improved if they were based on more precise area-based scores, such as census tracts. Still, a number of studies have repeatedly shown that using zip code-level measurements

results in estimates of socioeconomic gradients in health that are comparable but more conservative.⁴⁰

Conclusion

There is no doubt that weight reduction plays a key role in the incidence, prevalence, and overall health of CVD. Therefore, the utilization of AOMs could be a useful method to lessening the vast clinical burden of an incredibly prevalent disease in the U.S. The 8% relative risk reduction and lower prevalence of CVD outcomes demonstrated in this study indicates that AOM treatment could be an effective solution for alleviating the high prevalence of CVD. AOMs had a significant risk reduction in prevalent CVDs such as heart failure and atrial fibrillation. Our study adds to the literature of how AOMs are revolutionizing health care and can be a substantial solution for a prevalent disease like obesity, which is a significant risk factor for many debilitating conditions with high morbidity and mortality. Furthermore, we encourage future research to investigate whether the CVD risk reduction is attributable solely to weight loss (based on off-label use, as focused on in the present study) or to improved glucose control, alone or in combination with weight loss. It would also be of interest to investigate how payment type (ie, self-pay vs covered benefit) can impact the access to these medications and consequently cardiovascular outcomes of the population of patients with obesity.

DISCLOSURES

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Institutional Review Board Statement: The raw dataset on which this study is based is publicly available through a commercial data licensing agreement with Kythera labs. These data qualify as deidentified under HIPAA. The analysis of de-identified, publicly available data does not constitute human subjects research as defined by US Department of Health and Human Services 45 CFR 46.102 and does not require IRB review. Research involving collection or study of existing data, documents, and records can be exempted under Category 4 of the federal

regulations if: (i) the sources of such data are publicly available; or (ii) the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Informed Consent: Informed consent was not required as the data were from an anonymous, de-identified database compliant with HIPAA.

Data Availability: Data is not available due to privacy and ethical restrictions.

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Table 1. Baseline Characteristics Among AOM and Non-AOM Cohorts

Characteristics	With AOM (Ozempic or Wegovy or Mounjaro) (N = 5,926)		Without AOM (N = 79,118)		<i>P</i> Value	Std
	N/Mean	%/Std	N/Mean	%/Std		
Age group	71.53	4.47	73.67	5.65	<.0001	0.3821
65-70 years	2,925	49.36%	27,804	35.14%	<.0001	0.2968
71-80 years	2,739	46.22%	40,596	51.31%	<.0001	0.1019
80+ years	262	4.42%	10,718	13.55%	<.0001	0.2728
Gender						
Male	2,092	35.30%	30,738	38.85%	<.0001	0.0729
Female	3,834	64.70%	48,380	61.15%	<.0001	0.0729
Comorbidity Score						
CCI ≥ 2	2,969	50.10%	20,009	25.29%	<.0001	0.5645
CDS ≥ 2	4,800	81.00%	29,613	37.43%	<.0001	0.9113
Elixhauser Index ≥ 2	5,368	90.58%	54,347	68.69%	<.0001	0.4823
SES						
Low	1,998	34.35%	25,581	32.93%	0.0262	0.0302
Medium	1,875	32.23%	25,662	33.03%	0.2119	0.0170
High	1,944	33.42%	26,448	34.04%	0.3331	0.0132
Baseline CVD-related comorbidities						
Hypertension	4,293	72.44%	48,321	61.07%	<.0001	0.2345
Hyperlipidemia	2,316	39.08%	24,070	30.42%	<.0001	0.1874
Type 2 diabetes	3,842	64.83%	20,125	25.44%	<.0001	0.8983
COPD	405	6.83%	4,895	6.19%	0.0468	0.0268
Smoking history	440	7.42%	4,993	6.31%	0.0007	0.0456

Alcohol use disorder	33	0.56%	550	0.70%	0.2133	0.0168
Chronic kidney disease	195	3.29%	1,785	2.26%	<.0001	0.0686

AOM: anti-obesity medications; CCI: Charlson comorbidity index; CDS: Chronic Disease Score;

COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; SES:

socioeconomic status; STD: standardized difference.

Table 2. Unadjusted Outcomes Measures Among Patients in AOM and Non-AOM Cohorts

CVD	With AOM (Ozempic, Wegovy, or Mounjaro) (N = 5,926)		Without AOM (N = 79,118)		<i>P</i> Value	Std
	N/Mean	%/Std	N/Mean	%/Std		
Coronary artery disease	569	9.60%	7,355	9.30%	0.4352	0.0105
Heart failure	290	4.89%	4,848	6.13%	0.0001	0.0518
Atrial fibrillation	227	3.83%	4,091	5.17%	<.0001	0.0611
Arrhythmia	207	3.49%	3,276	4.14%	0.0153	0.0327
Ischemic heart disease	20	0.34%	160	0.20%	0.0289	0.0294
Stroke	107	1.81%	1,376	1.74%	0.7063	0.0051
Peripheral vascular disease	174	2.94%	2,721	3.44%	0.0395	0.0277
Any CVD	1,147	19.36%	16,745	21.16%	0.0010	0.0444

Abbreviations: AOM, anti-obesity medications; CVD, cardiovascular disease; Std, standardized difference.

Table 3. Cox Regression Results for Time to CVD (Hazard Ratio)

	HR	Confidence Interval		p-value
		Lower	Upper	
Treatment				
Yes	0.92	0.86	0.98	0.0068
No	1.00	1.00	1.00	
Characteristics				
Age Group: 65-70	1.00	1.00	1.00	
Age Group: 71-80	0.67	0.64	0.70	<.0001
Age Group: 80+	2.01	1.92	2.10	<.0001
Gender				
Female	0.74	0.72	0.77	<.0001
Male	1.00	1.00	1.00	
Comorbidity Scores				
Charlson Comorbidity Score (≥ 2)	1.40	1.34	1.45	<.0001
Chronic Disease Score (≥ 2)	1.12	1.08	1.15	<.0001
Elixhauser Score (≥ 2)	0.98	0.94	1.02	0.3622
SES				
Low	1.09	1.05	1.13	<.0001
Medium	1.07	1.03	1.11	0.0003
High	1.00	1.00	1.00	
CVD- related Comorbidities				
Hypertension	0.99	0.95	1.03	0.5483
Hyperlipidemia	0.95	0.91	0.98	0.0012
Diabetes Type 2	0.98	0.95	1.02	0.4382
COPD	1.41	1.33	1.48	<.0001
Smoking Hx	1.12	1.06	1.19	0.0001
Alcohol Use Disorder	1.01	0.85	1.21	0.8995

Chronic Kidney Disease	1.17	1.07	1.27	0.0005
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Abbreviations: AOM, antiobesity medications; CDS, Chronic Disease Score; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HR, hazard ratio; SES, socioeconomic status.

Figure Captions

Figure 1. Study Period Diagram

Figure 2. Aalen's Additive Regression Results for Risk of CVD (cumulative effect of the use of AOMs over time)

X axis = cumulative coefficients; Y axis = time

Note: The Aalen's model, as described by Madadizadeh et al, is a non-parametric model in which the effects of covariates (constant or variable effect) upon baseline hazard are additive. The Aalen's model provides cumulative regression function plots (Aalen's plot) that display how the effects of covariates change over the time.⁴² For example, while the effect of a treatment on the development of CVD may not be significant in the Cox analysis, an additive model can reveal a significant effect in the first year, with the effect diminishing in subsequent years.

Abbreviations: CCI: Charlson Comorbidity Index; CDS: Chronic Disease Score; CVD: cardiovascular disease; ELIX: Elixhauser index score; SES: socioeconomic status.

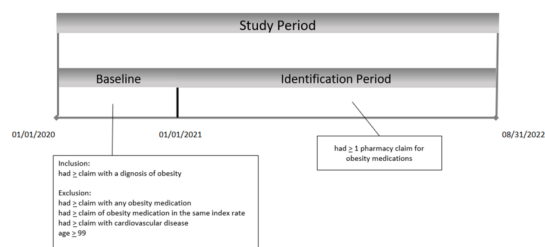


Figure 1 600 DPI.tif

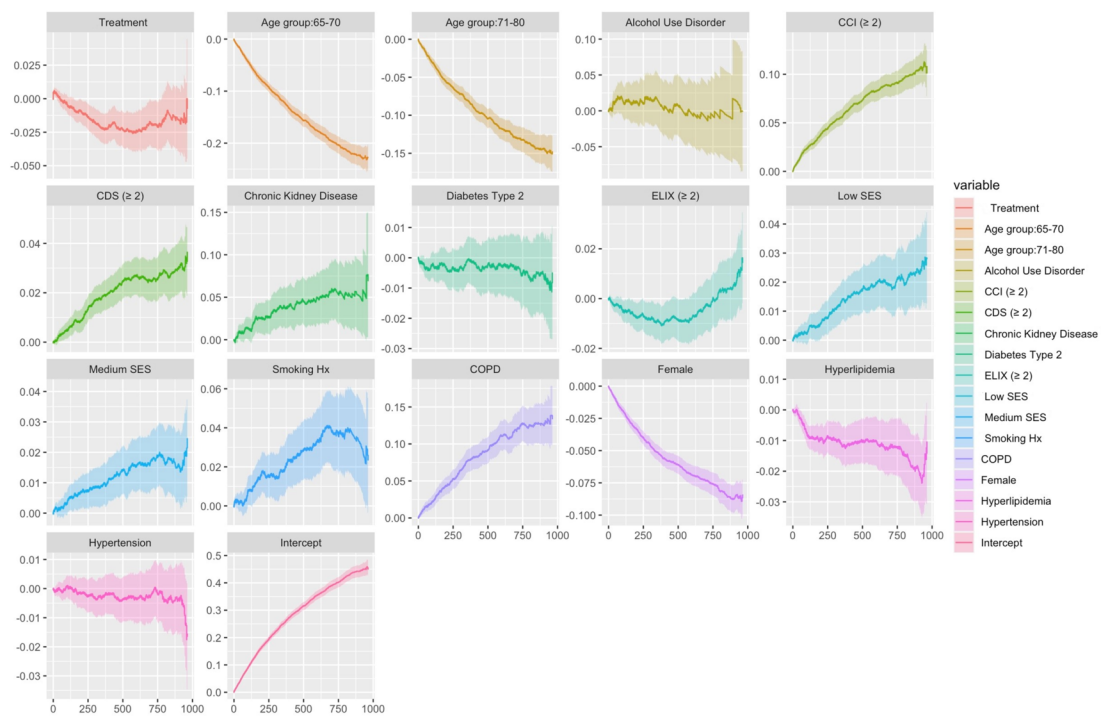


Figure 2 Updated_600DPI.tif