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Research article

Age and sex differences on anti-hyperglycemic medication exposure and risk of newly diagnosed multiple sclerosis in propensity score matched type 2 diabetics

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ABSTRACT

Background: The association between exposure to anti-hyperglycemic medications (A-HgM) for Type 2 Diabetes Mellitus (T2D) treatment and Multiple Sclerosis (MS) in T2D patients is unclear.
Methods: This retrospective cohort analysis used the Mariner claims database. Patient records were surveyed for a diagnosis of MS starting 12 months after diagnosis of T2D. Patients were required to be actively enrolled in the Mariner claims records for six months prior and at least three years after the diagnosis of T2D without a history of previous neurodegenerative disease. Survival analysis was used to determine the association between A-HgM exposure and diagnosis of MS. A propensity score approach was used to minimize measured and unmeasured selection bias. The analyses were conducted between January 1st and April 28th, 2021.
Findings: In T2D patients younger than 45, A-HgM exposure was associated with a reduced risk of developing MS (RR: 0.22, 95%CI: 0.17–0.29, p-value <0.001). In contrast, A-HgM exposure in patients older than 45 was associated with an increased risk of MS with women exhibiting greater risk (RR: 1.53, 95%CI: 1.39–1.69, $p < 0.001$) than men (RR: 1.17, 95%CI: 1.01–1.37, $p = 0 \cdot 04$). Patients who developed MS had a higher incidence of baseline comorbidities. Mean follow-up was 6.2 years with a standard deviation of 1.8 years.
Interpretation: In this study, A-HgM exposure in patients with T2D was associated with reduced risk of MS in patients younger than 45 whereas in patients older than 45, exposure to A-HgM was associated with an increased risk of newly diagnosed MS, particularly in women.

1. Introduction

Multiple sclerosis (MS) is an autoimmune-mediated neurological disorder that affects the central nervous system and leads to severe physical and cognitive disability. While the etiology of MS remains unclear, inflammation and demyelination are hallmarks of the disease [1, 2, 3, 4]. The main driver of pathology in MS is axonal loss and dysfunction due to the loss of the myelin sheath which are formed by oligodendrocytes in the central nervous system [3, 4].

While the etiology of MS is thought to be largely autoimmune the mechanisms driving disease conversion remain under debate [5]. Recent studies have shown a link between the onset of newly diagnosed MS and history of Type 1 and Type 2 Diabetes (T2D) [6, 7, 8]. In a study from Taiwan, patients with T2D were more likely to develop newly diagnosed MS (Hazard Ratio 1.44, Confidence Interval 1.09–1.94) [6]. It was hypothesized that this link is, in part, due to the underlying inflammatory basis of both diseases [6]. Further, insulin resistance has been shown to reduce myelin levels in the central nervous system, particularly in ApoE4 carriers [9]. There is mounting evidence linking metabolic disorders and MS through a common driver of increased autoimmunity which brings into question the impact of the therapeutics used to treat T2D on the incidence of MS.

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Anti-hyperglycemic medications (A-HgM) control glucose levels through different mechanisms [10, 11, 12, 13]. Based on their mechanism of action, A-HgM are divided into four major categories: (1) insulin sensitizers (biguanides and glitazones), (2) insulin secretagogues (sulfonylureas and meglitinides), (3) incretin analogues (GLP1 agonists and DPP4 inhibitors), and (4) insulin. In addition, injectable insulin is used in late-stage T2D patients who are not responding to other pharmacotherapies to directly activate the insulin receptor. These therapeutics target the immune system and each have distinct immunomodulatory profiles which may impact the pathogenesis of MS [13, 14, 15, 16].

Analyses reported herein were designed to determine potential associations between anti-hyperglycemic therapies used for T2D treatment and the incidence of MS across the aging spectrum in T2D patients. Our study was conducted using a US-based claims database that contains a significantly larger population than previously reported [13, 17, 18]. We further determined the impact of sex on MS incidence within this population. Additionally, we subdivided MS diagnoses based on age into early-onset MS (EOMS) and late-onset MS (LOMS). LOMS is defined by the diagnosis of MS over the age of 50, which represents between 2.7-12% of the patients with MS [19, 20, 21]. We report the association of individual anti-hyperglycemic agents within the A-HgM category with the risk of development of age-associated and primary MS.

2. Methods

2.1. Data source

This study used the Mariner dataset, an insurance claims database that includes patient health records from 122 million participants from 2010 to 2018. The database contains records from private-payer and Medicare insurance datasets across all US states and territories. The dataset includes demographic characteristics, prescription records, and other data points for patients with *Current Procedural Terminology*, *International Classification of Diseases, Ninth Revision (ICD-9)*, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes.

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was approved by the University of Arizona Institutional Review Board. Requirements for informed consent were waived as the data were deidentified.

2.2. Study design and variables

A subset of 5,283,017 participants with T2D were selected from the Mariner database. The outcome variable was defined as the occurrence of the first diagnosis of MS based on ICD-9 and ICD-10 codes in the participant's records (eTable1) 12 months after the index date. The index date is the first record of T2D diagnosis and the study start date is 12 months after the diagnosis of T2D. The diagnosis of MS was validated based on the previously published algorithms [22] in which a MS diagnosis is considered only in patients with >1 ICD codes (eTable1) and/or a drug claim for a disease modifying therapy for MS such as interferon beta-1a-SC, interferon beta-1a-IM, interferon beta-1b-SC, glatiramer acetate, fingolimod, natalizumab, dimethyl fumarate, and teriflunomide (eTable2). The treatment group was defined as patients having at least one A-HgM medication charge occurring after the diagnosis of T2D, including insulin, metformin, glitazones, sulfonylureas, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide (GLP-1) agonists, DPP4 inhibitors, glinides, or combination therapies (e.g., metformin and sulfonylureas) (eTable2). Drug groups with a low patient number were excluded from the analysis evaluating the association between MS and individual A-HgM drug classes. The median adherence and the median time between start of therapy and MS diagnosis are described in eTable3. The treatment group was then divided into individual A-HgM drug classes (eTable3). Participants with a diagnosis of T1D, with a history of neurosurgery or neurodegenerative disease (including MS) before the diagnosis of T2D were excluded from the study. An enrollment criterion of at least six months prior to and three years after diagnosis of T2D was applied (Figure 1). Age in the study is defined by the age at diagnosis of T2D. Following our previous studies [24, 25, 26, 27], an analysis of comorbidities known to be associated with MS outcomes was conducted. We then conducted sensitivity analyses to address the impact of age and sex in the study population.

2.3. Statistical analysis

Statistical analyses were performed between January 28th and April 28th, 2021. Patient demographic statistics (Table 1) and incidence statistics were analyzed using unpaired 2-tailed t-tests or $\chi 2$ tests, as appropriate, to test the significance of the differences between continuous and categorical variables. In all analyses, a 2-sided $P < 0.05$ was considered statistically significant.

A propensity score matching algorithm was applied to estimate the association between A-HgM and MS as previously described [23, 24, 25, 26, 27]. A logistic regression was used to estimate the probability for each participant to receive A-HgM given their age, gender, region, comorbidities, and Charlson Comorbidity Index (CCI) score. The propensity score matching included the variables that were statistically significant in the regression model (listed in eTable1) to reduce confounding factors in group assignment. The quality of the matching was assessed by standardized mean difference with percent balance improvement (eTable4).

Biological pathway analysis was conducted using a Drug-Target Interaction (DTI) network approach (eFigure2) as previously described [24]. For each drug identified, the related gene targets were extracted using DrugBank database [28].

3. Results

3.1. Study population

In the Mariner dataset, over 5 million patients with a diagnosis of T2D were identified (Figure 1). Two populations were evaluated separately: (1) those whose diagnosis of diabetes occurred prior to age 45 and (2) those whose diagnosis of diabetes occurred after age 45. In the younger population, 723,976 patients remained in this population after exclusion of patients with a diagnosis of T1D, a history of neurosurgery or brain cancer, a diagnosis of neurodegenerative disease (NDD), including MS, before the index date as well as those patients over the age of 45. Following propensity score matching, 287,226 patients from the young cohort remained in the study. Of the propensity score matched cohort, 143,613 (mean [standard deviation (SD)] age, 30.16 [2.43] years) patients controlled their diabetes through lifestyle (no record of receiving a medication for the treatment of hyperglycemia) whereas 143,613 (34.79 [1.02] years) patients had records of receiving a medication to control hyperglycemia (Figure 1).

In the older population, over 4 million patients remained in the population after the exclusion criteria described above except for the age exclusion, which in this case was patients younger than 45 years old (Figure 1). After enrollment and propensity score matching, the over 45 cohort was composed of 1,277,250 patients. Within the adjusted over 45 group, 638,625 (61.85 [6.19] years) patients were untreated whereas 638,625 (57.37 [5.56] years) patients had a record of receiving A-HgM (Figure 1).

Within the matched younger than 45 cohort, the majority of the patients were between 40 and 44 years old and 62% and 53% identified as female in the control and treatment group, respectively (Table 1). Most of the untreated patients were from the Northeast region of the US whereas the majority of the treated patients were from the South. For the older than 45 cohort, most of the untreated patients were female (55.6%) and most of the treated patients were male (50.5%) (Table 1). In both cohorts,

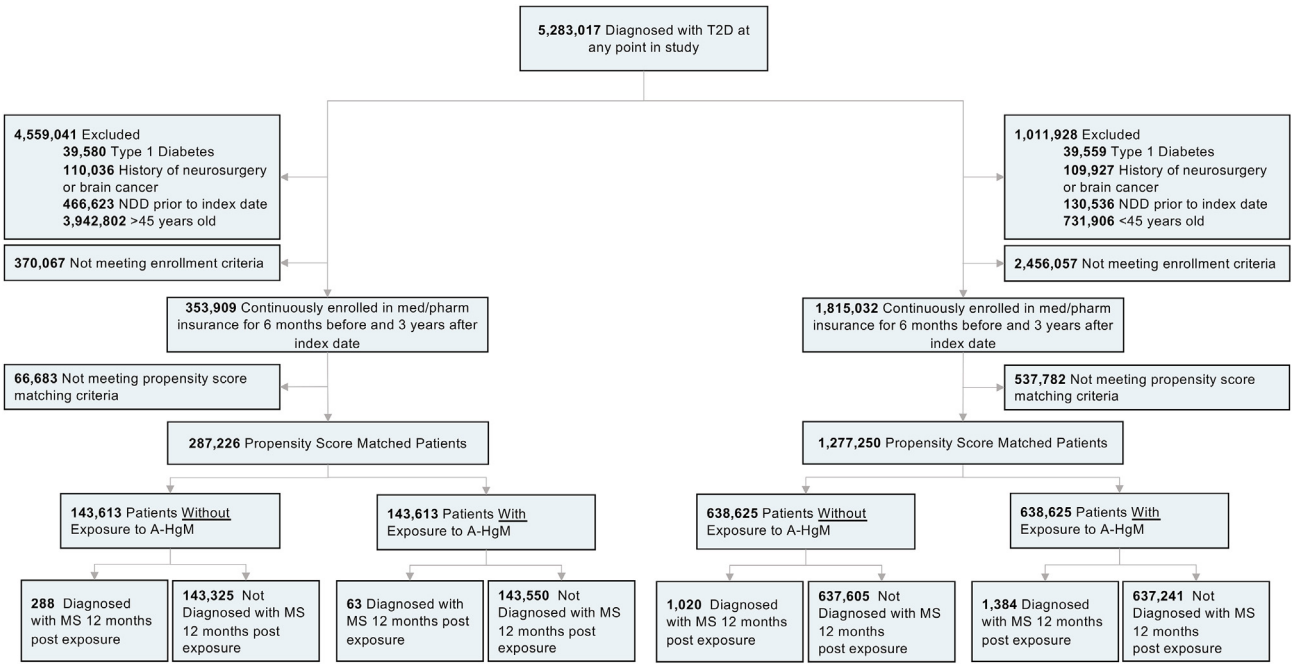

Figure 1. Study design and patient breakdown.

patients were predominantly from the South region of the US. The comorbidities and CCI of both cohorts are reported in Table 1. To address the severity of T2D, the number of A-HgM in the treated group was determined. In the younger cohort, 92,393 (64.33%) of patients were treated with 2 or less A-HgM drugs, 48,488 (33.76%) were treated with 3 drugs, and 2,732 (1.90%) were exposed to 4 drugs. Similarly, in the older cohort, 342,783 (56.68%) of patients were treated with 2 or less A-HgM drugs, 273,574 (42.84%) were exposed to 3 drugs, and 22,268 (3.49%) were exposed to 4. In the younger population, the median time duration (median [SD]) of T2D in the control group was 6.0 [1.8] years and in the treated group was 6.6 [1.9] years. In the older population, the median time duration of the diagnosis in the control group was 6.0 [1.8] years and in the treated group was 7.29 [1.8] years.

3.2. Risk analysis

In both unadjusted population and propensity score matched (PSM) population, the overall risk for newly diagnosed MS in patients under 45 years of age was reduced in the population receiving A-HgM (unadjusted: Relative Risk (RR): 0.27, 95% Confidence Interval (CI): 0.21–0.33, p value (p) < 0.001); PSM: RR: 0.22, 95% CI: 0.17–0.29, $p < 0.001$) (Table 2, eFigure1). Conversely, in the older than 45 years old cohort, the risk of developing MS was increased in both unadjusted and PSM populations with A-HgM exposure (unadjusted: RR: 1.16, 95% CI: 1.10–1.23, $p < 0.001$); PSM: RR: 1.36, 95% CI: 1.25–1.47, $p < 0.001$) (Table 2, eFigure1).

When individual A-HgM drug classes were evaluated in the population under 45 years of age at MS diagnosis, sulfonylureas alone or in combination with metformin were significantly associated with a decreased incidence of MS (Sulfonylureas: RR: 0.11, 95% CI: 0.06–0.19, $p < 0.001$; Metformin&Sulfonylureas: RR: 0.11, 95% CI: 0.06–0.20, $p < 0.001$). All other A-HgM drugs classes provided comparable reduction in risk (Figure 2). In the over 45 cohort, when individual A-HgM classes were evaluated to determine any association with the incidence of newly diagnosed late-onset MS (LOMS), A-HgM exposure was associated with an increased risk of MS in all drug classes. Importantly, insulin exposure (RR: 1.84, CI: 1.67–2.02, $p < 0.001$) was found to be associated with a significantly increased incidence over the other therapeutic groups (Figure 2). Consistent with the drug class indications, A-HgM therapeutic targets were predominately driven by class type (DPP4 inhibitors vs Glitazones vs Metformin) with only pioglitazone and glipizide targeting overlapping pathways beyond their drug class (eFigure2).

When evaluating the impact of sex in both age cohorts, there were differences in the incidence of disease (Figure 3, eTable5). For patients aged younger than 45 years old, both men and women treated with A-HgM exhibited a decreased risk for incidence of MS (Men: RR: 0.17, CI: 0.09–0.32, $p < 0.001$; Women: RR: 0.28; CI: 0.21–0.37; $p < 0.001$). For men older than 45 years old, A-HgM exposure had a slightly significant increase on MS risk (RR: 1.17, CI: 1.01–1.37, $p = 0.04$) whereas women older than 45 years exhibited a significant increase of MS incidence compared to control (RR: 1.53, CI: 1.39–1.69, $p < 0.001$) (Figure 3, eTable5).

To address the potential clinical drivers of the sex difference, we conducted a responder analysis in the younger and older than 45 aged cohorts to identify factors associated with a diagnosis of MS in each population (eTable6&7). In both cohorts, those patients who developed MS, or non-responders, had an overall higher incidence of comorbidities than responders (did not develop MS) after exposure to A-HgM. In the younger than 45 cohort, non-responders had a higher incidence of asthma and cardiovascular comorbidities whereas in the older than 45 cohort, asthma, chronic kidney disease, and stroke were the most prevalent comorbidities among non-responders. In general, patients who developed MS (non-responders) were predominantly women (eTable6&7).

4. Discussion

This study aimed to identify and describe the association between exposure to anti-hyperglycemic therapies used for the treatment of Type 2 Diabetes Mellitus and the incidence of Multiple Sclerosis in younger and older than 45 aged cohorts. Additional analyses of sex difference in MS incidence were conducted to elucidate factors driving MS risk in these populations. To our knowledge, this is the largest and most comprehensive study to-date to examine the impact of individual anti-hyperglycemic therapies on MS risk. Notably, the results of these analyses indicated that both age and sex regulate response to A-HgM exposure to impact MS risk profiles.

Table 1. Baseline characteristics for propensity score-matched T2D patients* younger and older than 45 Years old with or without exposure to A-HgM.

	<45 years old					>45 years old				
	Without Exposure to A-HgM		With Exposure to A-HgM			Without Exposure to A-HgM		With Exposure to A-HgM		
	N	%	n	%		n	%	n	%	
Number of Patients	*143,613*		*143,613*		***p value***	*638,625*		*638,625*		***p value***
Age										
<2	503	*0.35%*	1	*0.00%*	<0.001					
02 to 04	1,805	*1.26%*	16	*0.01%*						
05 to 09	2,956	*2.06%*	206	*0.14%*						
10 to 14	4,155	*2.89%*	1,326	*0.92%*						
15 to 19	7,309	*5.09%*	2,723	*1.90%*						
20 to 24	12,966	*9.03%*	4,235	*2.95%*						
25 to 29	17,405	*12.12%*	9,384	*6.53%*						
30 to 34	23,742	*16.53%*	21,335	*14.86%*						
35 to 39	31,041	*21.61%*	38,873	*27.07%*						
40 to 44	41,731	*29.06%*	65,514	*45.62%*						
45 to 49						56,143	*8.79%*	95,436	*14.94%*	*<0.001*
50 to 54						75,565	*11.83%*	118,983	*18.63%*	
55 to 59						87,529	*13.71%*	122,695	*19.21%*	
60 to 64						91,189	*14.28%*	107,415	*16.82%*	
65 to 69						93,519	*14.64%*	88,463	*13.85%*	
70 to 74						153,805	*24.08%*	93,780	*14.68%*	
75 to 79						80,875	*12.66%*	11,853	*1.86%*	
Gender										
Female	89,563	*62.36%*	77,325	*53.84%*	*<.001*	355,008	*55.59%*	316,286	*49.53%*	*<0.001*
Male	54,050	*37.64%*	66,288	*46.16%*		283,617	*44.41%*	322,339	*50.47%*	
Region										
Midwest	22,843	*15.91%*	41,818	*29.12%*	*<0.001*	115,866	*18.14%*	177,665	*27.82%*	*<0.001*
Northeast	61,137	*42.57%*	5,246	*3.65%*		197,689	*30.96%*	33,773	*5.29%*	
South	45,382	*31.60%*	72,158	*50.24%*		242,852	*38.03%*	314,871	*49.30%*	
West	13,938	*9.71%*	24,202	*16.85%*		81,229	*12.72%*	111,137	*17.40%*	
Unknown	313	*0.22%*	189	*0.13%*		989	*0.15%*	1,179	*0.18%*	
Comorbidities										
Asthma	3,342	*2.33%*	9,190	*6.40%*	*<0.001*	3,573	*0.56%*	1,389	*0.22%*	*<0.001*
COPD	1,031	*0.72%*	2,116	*1.47%*	*<0.001*	7,058	*1.11%*	2,387	*0.37%*	*<0.001*
Chronic Kidney Disease	1,454	*1.01%*	6,789	*4.73%*	*<0.001*	9,944	*1.56%*	4,382	*0.69%*	*<0.001*
Congestive Heart Failure	1,294	*0.90%*	3,879	*2.70%*	*<0.001*	11,956	*1.87%*	4,966	*0.78%*	*<0.001*
Coronary Artery Disease	2,673	*1.86%*	7,572	*5.27%*	*<0.001*	23,874	*3.74%*	15,499	*2.43%*	*<0.001*
Hypertension	13,977	*9.73%*	50,036	*34.84%*	*<0.001*	53,293	*8.34%*	51,959	*8.14%*	*<0.001*
Ischemic Heart Disease	2,505	*1.74%*	6,293	*4.38%*	*<0.001*	23,484	*3.68%*	15,360	*2.41%*	*<0.001*
Obesity	10,928	*7.61%*	39,909	*27.79%*	*<0.001*	18,079	*2.83%*	18,191	*2.85%*	*0.55*
Osteoarthritis	3,538	*2.46%*	8,514	*5.93%*	*<0.001*	26,365	*4.13%*	14,140	*2.21%*	*<0.001*
Pulmonary Heart Disease	969	*0.67%*	2,766	*1.93%*	*<0.001*	5,195	*0.81%*	1,797	*0.28%*	*<0.001*
Rheumatoid Arthritis	959	*0.67%*	638	*0.44%*	*<0.001*	3,058	*0.48%*	501	*0.08%*	*<0.001*
Stroke	1,231	*0.86%*	2,584	*1.80%*	*<0.001*	12,676	*1.98%*	4,450	*0.70%*	*<0.001*
Tobacco Use	6,562	*4.57%*	15,626	*10.88%*	*<0.001*	14,358	*2.25%*	6,770	*1.06%*	*<0.001*
CCI										
0–4	138,291	*96.29%*	143,139	*99.67%*	*<0.001*	586,371	*91.82%*	635,303	*99.48%*	*<0.001*
5–10	5,067	*3.53%*	474	*0.33%*		48,527	*7.60%*	3,322	*0.52%*	
11+	255	*0.18%*	-	*0.00%*		3,727	*0.58%*	-	*0.00%*	

Our results indicate two distinct risk profiles in patients younger versus older than 45 years of age. A-HgM exposure in patients younger than 45 was protective against the development of MS (Table 2, eFigure1). Conversely, in patients older than 45 A-HgM exposure was associated with increased risk of MS, particularly in women and less so in men (Table 2, eFigure1). To determine whether drugs within the A-HgM class were driving these risk profiles, we conducted analyses of each drug class (Figure 2). These results indicated that the MS risk profiles were driven by age more than by drug class. This may, in part, be due to the subtype of MS that is predominately diagnosed in these age groups. Relapsing remitting MS (RRMS) is the most common subtype of in patients between 20-40 years of age [5, 29] (approximately 87%) [5] which is characterized by unpredictable acute attacks followed by periods of remission and is diagnosed predominately. Prior to the 1980s in the United States, a diagnosis of MS excluded adults over 50 years of age [21, 30]. More recently, late-onset Multiple Sclerosis (LOMS) has been recognized, which is often characterized by primary progressive course of disease with pyramidal or cerebellar involvement observed in 60%–70% of the patients at presentation [29]. Given the relatively recent acceptance of LOMS, there are a limited number of studies [19, 20, 21]

Table 2. Incidence and relative risk of T2D patients receiving anti-hyperglycemic medication to develop MS.

	<45 yo Cohort	>45 yo Cohort
Unadjusted Cohort		
Patients not receiving A-HgM	*288*	*1,670*
%	0.20%	0.26%
Patients receiving A-HgM	*112*	*3,579*
%	0.05%	0.30%
Relative Risk	*0.27*	*1.16*
95%CI	0.21–0.33	1.10–1.23
NNT	679 · 1	2340
p-value	*<0.001*	*<0.001*
Propensity Score-Matched Cohort		
Patients not receiving A-HgM	*288*	*1,020*
%	0.20%	0.16%
Patients receiving A-HgM	*63*	*1,384*
%	0.04%	0.22%
Relative Risk	*0.22*	*1.36*
95%CI	0.17–0.29	1.25–1.47
NNT	638.3	1754
p-value	*<0.001*	*<0.001*

investigating the mechanisms of disease driving MS in an aging population. In addition to age differences, the risk analysis by drug class showed that exposure to insulin in patients older than 45 years old was associated with a greater increased risk compared to other therapies. This can be explained, in part, by severity of the disease, glycemic control or socioeconomic status of patients receiving insulin.

Within an age cohort, we also sought to identify the impact of sex on MS risk after A-HgM exposure. It is known that women are disproportionately affected by MS and that there are a number of sex specific aspects of MS including disease risk, disease expression and prognosis [31, 32, 33]. A study from Denmark showed that the incidence of MS in women has doubled (comparing 1950–1959 to 2000–2009 data), compared to a smaller increase noted in men [34]. Of interest, the incidence of LOMS increased 4.30 fold in women and 2.72 fold in men over the same time period [34]. In our study, in the younger than 45 cohort, no sex difference was observed in response to A-HgM exposure, which was associated with a decreased risk of MS in both men and women under 45 years old (Figure 3). In contrast, A-HgM exposure in the older than 45 cohort was associated with a small but significant increased risk of MS in men, whereas the use of A-HgM in women was associated with a substantial increase in the risk of developing MS (Figure 3).

This observation may be explained by a variety of factors resulting from immune system changes that occur during the perimenopause-to-menopause transition in this population of women. Each year ~1.5 million American women enter into perimenopause, a midlife neuroendocrine transition state unique to the female [35]. It is well-known that the female immune response is more robust than that in the male [36]. This is, in part, the reason for the increased propensity for females to develop autoimmune diseases. Epidemiological and biochemical evidence suggest a role for female sex hormones to drive this dichotomy. With the fall of estrogen at menopause, there is an increase in pro-inflammatory cytokines, including interleukin (IL)-6, IL-8, and tumor necrosis factor [37, 38]. Further, there are observed increases in CD4/CD8 ratios, T cell activation, B cells and immunoglobulin in women at menopause [39, 40, 41]. Substantial evidence indicates that female menopause leads to a chronic low grade pro-inflammatory state [37, 40], bioenergetic crisis in brain [35, 41], catabolism of white matter as an auxiliary fuel source of fatty acids [42], a rise in autoimmune signaling [38], decline in white matter volume [43] and increased symptoms of MS after menopause [37, 40, 41].

It is known that diabetes, similar to MS, is linked to a proinflammatory state [44] and that symptomatic worsening in female diabetics occurs during menopause due to loss of estrogenic control of insulin sensitivity and resistance [45, 46, 47]. During this menopausal transition, glucose fluctuations result in oxygen radical production and inflammation, both systemically and in the brain, which may contribute to an increased risk of MS [48]. The impact of A-HgM exposure in pro-inflammatory postmenopausal diabetic patients is both interesting and concerning.

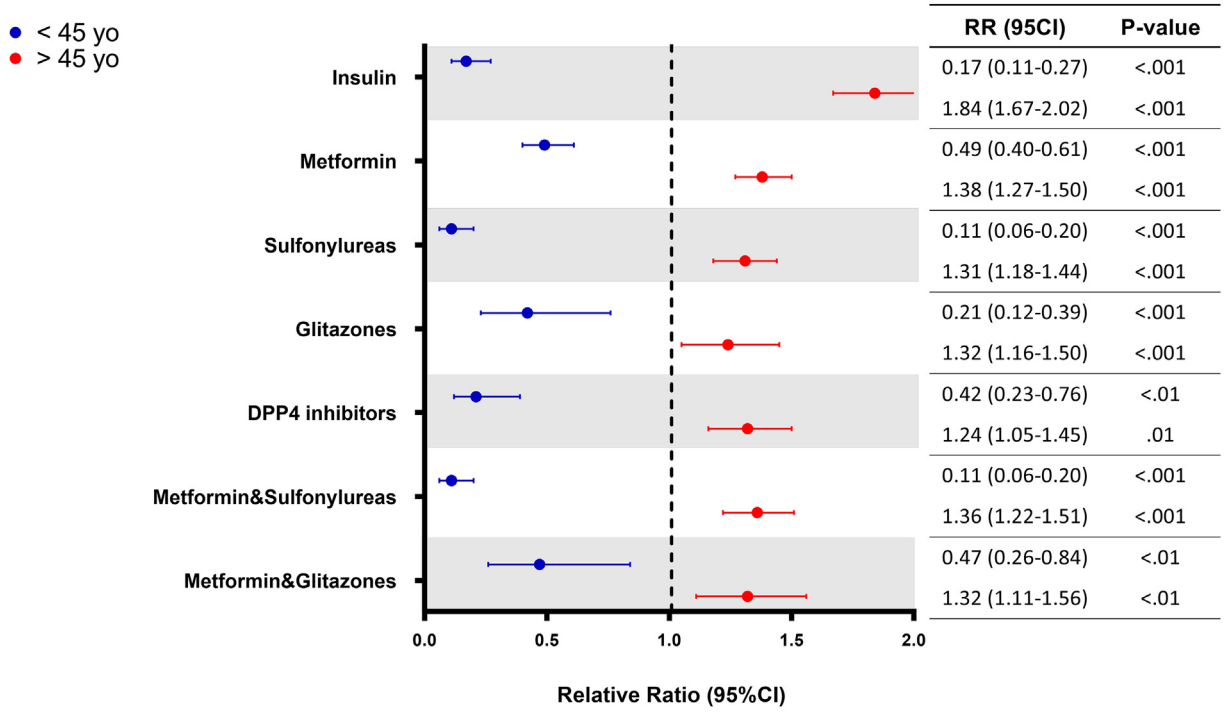

Figure 2. Relative risk of propensity score-matched T2D patients younger and older than 45 years old with exposure to different A-HgM to develop MS.

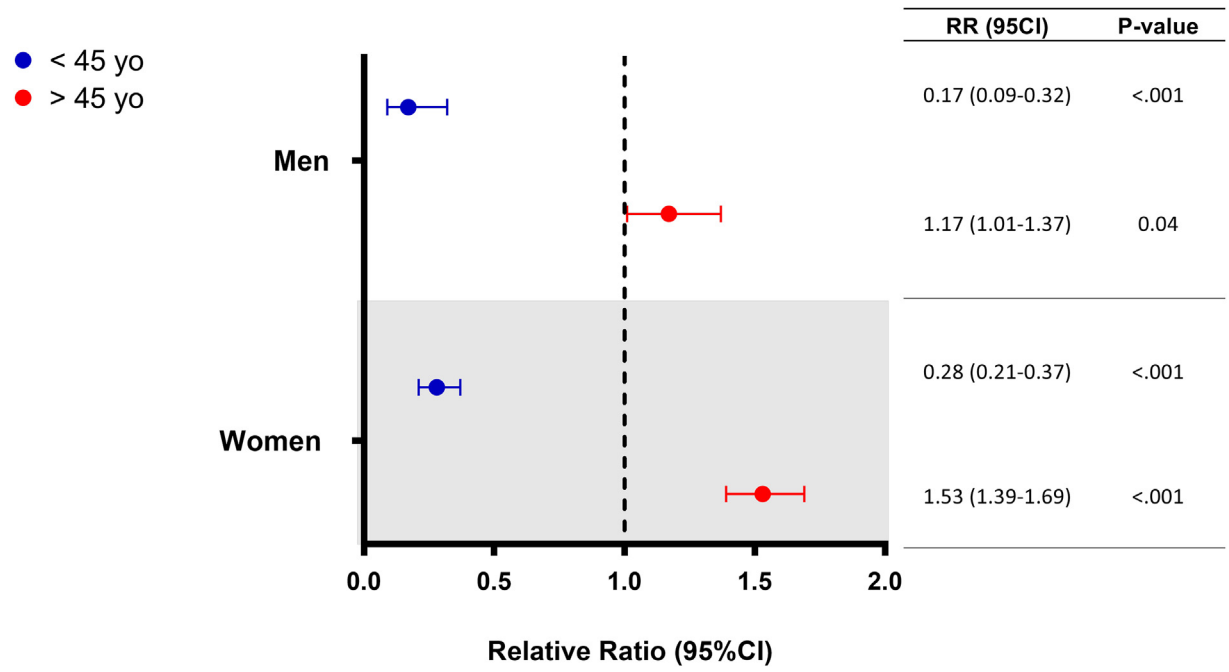

Figure 3. Sex differences in the relative risk of propensity score-matched T2D patients younger and older than 45 years old with exposure to A-HgM to develop MS.

The geographic/longitudinal risk factors for the development of MS are well documented [49]. In our populations, the majority of people who control their T2D with diet/exercise (non-treatment group) are located in the Northeast region of the US where there is an association with a greater incidence of MS (Table 1). Important to consider is the fact that the T2D population potentially represents a unique subset of patients with MS. Thus, the incidence of MS and its etiology in the context of T2D may not exactly follow the prevalence of MS in a general population. It also follows that since T2D is an age-associated disease (increased prevalence with increased age), the population of T2D patients will be larger for those older than 45 years of age. However, the incidence of MS is still greater in the younger cohort when accounting for total population, which is consistent with national trends and data for MS prevalence [29]. This study aimed to identify the association between MS risk and commonly used A-HgM in an at-risk population, which contribute to the Brain Health recommendations for MS prevention, where brain and cognitive reserves must be preserved to maximize long-term brain health [50].

4.1. Limitations

Participants included in this study may have obtained services outside of those included in this database. This study relied on ICD codes assigned by a physician and lab values such as glucose levels were not used to confirm a diagnosis of T2D. Drug prescribing trends, lifestyle changes, as well as switching/overlap of A-HgM were not included in this analysis. Although the propensity-score matching addressed most confounding factors, there could be factors addressed inadequately by this method. Subtype of MS or disability level of each MS patient could not be assessed in this cohort. Genetic data and latitude information relevant to MS were not available in this dataset.

5. Conclusion

Exposure to anti-hyperglycemic medication was associated with a reduced incidence of MS in T2D patients younger than 45. Conversely, in patients older than 45 years old, anti-hyperglycemic agents were associated with an increased risk of developing MS, particularly in women. It will become increasingly important to understand the neuro-immunological changes that occur during the perimenopause transition and how these changes may affect brain health and disease risk in aging populations. These findings represent an important call to action for better understanding the interplay between the endocrine, immune, and nervous systems and the need for a precision medicine approach for prevention of multiple sclerosis in vulnerable populations.

Declarations

Author contribution statement

Branigan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Torrandell-Haro and Vitali: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Brinton and Rodgers: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

The data that has been used is confidential.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2022.e11196.

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