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Research: Epidemiology

Use of antidiabetic and antidepressant drugs is associated with increased risk of myocardial infarction: a nationwide register study

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Abstract

Aims To explore the gender- and age-specific risk of developing a first myocardial infarction in people treated with antidiabetic and/or antidepressant drugs compared with people with no pharmaceutical treatment for diabetes or depression.

Methods A cohort of all Swedish residents aged 45–84 years (n = 4 083 719) was followed for a period of 3 years. Data were derived from three nationwide registers. The prescription and dispensing of antidiabetic and antidepressant drugs were used as markers of disease. All study subjects were reallocated according to treatment and the treatment categories were updated every year. Data were analysed using a Cox regression model with a time-dependent variable. The outcome of interest was first fatal or non-fatal myocardial infarction.

Results During follow-up, 42 840 people had a first myocardial infarction, 3511 of which were fatal. Women aged 45–64 years, receiving both antidiabetic and antidepressant drugs had a hazard ratio for myocardial infarction of 7.4 (95% CI 6.3–8.6) compared with women receiving neither. The corresponding hazard ratio for men was 3.1 (95% CI 2.8–3.6).

Conclusions The combined use of antidiabetic and antidepressant drugs was associated with a higher risk of myocardial infarction compared with use of either group of drugs alone. The increase in relative risk was greater in middle-aged women than in middle-aged men.

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Introduction

Diabetes mellitus is among the leading causes of death and disease burden globally [1] and its prevalence is increasing worldwide, with most of the increase in developing countries [2]. Psychosocial risk factors and depressive disorders often co-occur with general medical comorbidities, such as myocardial infarction (MI) [3–5], and depression is more common in patients with diabetes than in patients without diabetes. Approximately 10–30% of people with diabetes also have a depressive disorder, which is double the estimated prevalence of depression in people without diabetes [1,6–9]. Previously, it has been shown that there is a weak relationship between diabetes and impaired glycaemic control in adults with diabetes and coexistent depression [10]; however, there is a stronger association between comorbid depressive symptoms and diabetes complications, such as nephropathy, neuropathy and macrovascular complications [11]. This is believed to be mainly attributable to poor adherence to treatment recommendations and diabetes self-management activities [7], but could also possibly have biological and behavioural causes that could predispose to both metabolic and affective disorders [11]. People with comorbid diabetes and depression respond to antidepressive treatment to the same extent as those with depression but without diabetes [12].

It has been also been shown that people with comorbid diabetes mellitus and depression have a higher prevalence of coronary heart disease and risk of death compared with those who have either of the conditions alone [1,6]. The risk of MI is strongly dependent on age and sex, with men having an

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What's new?

- Our data show that middle-aged women treated with glucose-lowering agents and antidepressants have a substantially higher relative risk of a first fatal or non-fatal myocardial infarction compared with middle-aged men treated with glucose-lowering agents and antidepressants.
- Linkage of nationwide population-based register data on diseases and drugs is useful for numerous analyses and, because of its scale, also provides valid subgroup estimates.
- Diabetes risk factor control is particularly important in patients with diabetes combined with depression to prevent cardiovascular complications.

earlier disease onset than women [13]. Data on all dispensed drug prescriptions in Sweden are available in the Swedish Prescribed Drug Register and all cases of MI are registered in the Myocardial Infarction Statistics. These registers are population-based, have complete national coverage and have been shown to have high validity [14]. The large quantity of data allows valid estimates for subgroups and the registries are therefore useful for stratified analyses. Currently, to the best of our knowledge, there are no studies exploring the age- and gender-specific risk of MI attributable to diabetes with coexistent depression. In the present study we used treatment with antidiabetic and/or antidepressant drugs as markers for diabetes and depression. Our objective was to explore prospectively the gender- and age-specific risk of first MI in people treated with antidiabetic and/or antidepressant drugs compared with people with no pharmaceutical treatment for diabetes or depression in a nationwide register study.

Subjects and methods

A cohort of all Swedish residents aged 45–84 years old (n = 4 083 719) was followed in an individual-level study through the use of two population-based nationwide registers: the Swedish Prescribed Drug Register (National Board of Health and Welfare) [15] and the Myocardial Infarction Statistics (National Board of Health and Welfare)

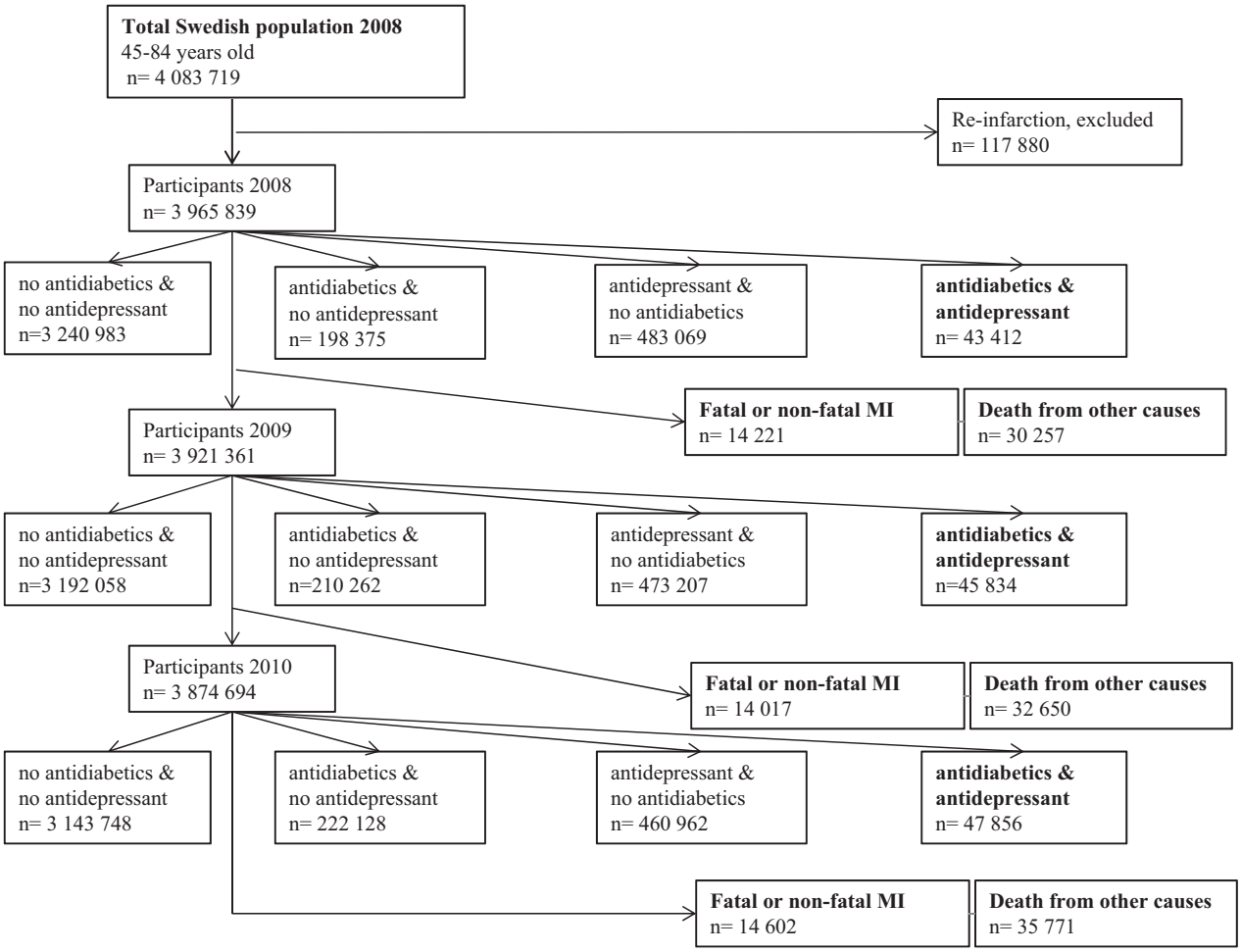

FIGURE 1 Study flow chart. MI, myocardial infarction.

Table 1 Total population in Sweden in 2008 and the 3-year incidence of first myocardial infarction, stratified by gender and age

Age	Gender	Total population January 2008 *n*	Total population with no re-infarction January 2008 *n*	First MI January 2008 to December 2010 *n*	%
45–64 years	Men	1 233 273	1 217 478	9 824	0.8
	Women	1 209 995	1 202 663	3 174	0.3
65–84 years	Men	783 070	725 815	18 160	2.5
	Women	857 381	819 883	11 682	1.4
45–84 years	Men	2 016 343	1 943 293	27 984	1.4
	Women	2 067 376	2 022 546	14 856	0.7

MI, myocardial infarction.

Table 2 Cases of first myocardial infarction per 1000 person-years in the Swedish population from January 2008 to December 2010, stratified by gender, age and treatment for diabetes and/or depression

Age	Gender	Treatment	First MI, Cases per 1000 person-years
45–64 years	Men	Antidiabetic and antidepressant drugs	7.6
		Antidepressant drugs and no antidiabetic drugs	3.3
		Antidiabetic and no antidepressant drugs	6.0
		No antidiabetic and no antidepressant drugs	2.5
	Women	Antidiabetic and antidepressant drugs	5.4
		Antidepressant drugs and no antidiabetic drugs	1.2
		Antidiabetic and no antidepressant drugs	3.7
		No antidiabetic and no antidepressant drugs	0.7
65–84 years	Men	Antidiabetic and antidepressant drugs	16.2
		Antidepressant drugs and no antidiabetic drugs	9.2
		Antidiabetic and no antidepressant drugs	12.6
		No antidiabetic and no antidepressant drugs	7.9
	Women	Antidiabetic and antidepressant drugs	13.3
		Antidepressant drugs and no antidiabetic drugs	5.6
		Antidiabetic and no antidepressant drugs	10.3
		No antidiabetic and no antidepressant drugs	4.0
45–84 years	Men and women	Antidiabetic and antidepressant drugs	12.3
		Antidepressant drugs and no antidiabetic drugs	5.4
		Antidiabetic and no antidepressant drugs	9.9
		No antidiabetic and no antidepressant drugs	4.3

MI, myocardial infarction.

[16]. The latter is based on information from the Cause of Death Register (National Board of Health and Welfare) and the National Patient Register (National Board of Health and Welfare) and holds information on first MI and re-infarctions during 2005–2010. From these registers, we obtained dates, unique personal identification number, diagnosis according to the International Classification of Diseases, 10th version, dispensed pharmaceuticals according to the Anatomical, Therapeutic and Chemical (ATC) classification system [17] and data on first fatal or non-fatal MI. Patient records were anonymized and de-identified before the analysis of data. The cohort was stratified according to gender and age.

To render a complete database on all Swedish residents in the age span and with no re-infarction during 2005–2010, the individuals obtained from the individual-level registers for antidiabetic and antidepressive treatment and diagnosis for MI were subtracted from the total number of individuals acquired from the Total Population Register (Statistics Sweden)[18]. Individuals who had a re-infarction during the study period, 2005–2010, were excluded.

Dispensed antidiabetic (ATC code A10), antidepressant (ATC code N06A) and antihypertensive drugs (ATC codes C03 and C07-09) were used as markers of disease. Figure 1 shows the categorization of all study subjects according to treatment with drugs for diabetes and depressive disorders. The cohort was followed for 3 years, from January 2008 to December 2010. There was a run-in period of 2 years and participants were classified in four treatment categories: 1) antidiabetic and antidepressant treatment combined; 2) antidepressive treatment only; 3) antidiabetic treatment only; or 4) neither antidiabetic nor antidepressant treatment. Subjects were reallocated to one of these treatment groups in 2009 and 2010. The classification was based on dispensing of antidiabetic and/or antidepressant drugs on at least one occasion during the previous 2 years.

For statistical analysis, a Cox regression model was used, with time from January 2008 to first fatal or non-fatal MI event recorded as the follow-up time variable. Subjects with no MI event were censured at time of death or end of the follow-up period (December 2010). Treatment category was treated as a time-dependent variable. Hazard ratio (HR) estimates with 95% CIs were computed using the Cox regression model for the three categories of antidiabetic and/or antidepressant drug use (category 1, 2 and 3) compared with a reference group without glucose-lowering agents or antidepressant treatments (category 4). Subjects were stratified by gender and age group (45–64 years and 65–84 years).

The study complied with the Declaration of Helsinki and was approved by the Regional Ethical Review Board at Linköping University, Linköping, Sweden (2011/489-31.)

Results

Of the total population without re-infarction (n = 3 965 839) in year 2008 at baseline, 241 787 subjects (6.1%) had received antidiabetic drugs and 526 481 (13.3%) subjects had received antidepressant drugs. Antidiabetic drugs were more common in men: 121 156 men (6.2%) had treatment compared with 77 219 women (3.8%). The use of antidepressants was almost twice as common in women; 324 256 women (16.0%) were treated compared with 158 813 men (8.2%) at baseline. During follow-up, 42 840 subjects (1.1%) had a first MI, of which 3511 (8.2%) were fatal. The incidence of all-cause mortality was 103 660 (2.6%) during the 3-year study period.

Table 1 shows the incidence of first fatal or non-fatal MI for all Swedish residents aged 45–84 years, stratified by age and gender. MI was more frequent in men than in women; the overall MI incidence in men was double that of women, and men were also younger than women at the time of first MI.

Table 2 shows the incidence of first MI during follow-up per 1000 person-years, according to the diabetes status and treatment for depression. The results were stratified by gender and by age groups (46–64 years and 65–84 years). The incidence of first MI was highest in subjects with combined antidiabetic and antidepressant treatment compared with no treatment, or treatment with either antidepressant or antidiabetic drugs in all categories: men, women, age 45–64 years and age 65–84 years.

Figure 2 shows the crude HRs and 95% CIs for a first MI compared with the reference group; i.e. subjects without treatment for diabetes or depression, stratified by age and gender. Women with antidiabetic and antidepressant drugs in the age category 45–64 years had a substantially greater HR for MI (7.4, 95% CI 6.3–8.6) compared with men (3.1 95% CI 2.8–3.6) in the same age category. When the analyses were adjusted for antihypertensive medication the results remained virtually unchanged.

Discussion

We conclude from this population-based, nationwide register study of 3 965 839 people, that the combination of pharmacologically treated diabetes and use of antidepressant drugs substantially increased the risk of a first MI compared with treatment of neither or either of the conditions alone. This is consistent with previously reported data [19]; however, there were some gender-specific differences. The HR for having a first MI for women 45–64 years with both depression and diabetes, was more than seven times higher compared with women with neither diabetes nor depression. The corresponding HR in men was 3.1.

In the general population women are at much lower risk of ischaemic heart disease mortality than men; however, it is widely held that women with diabetes are at especially high risk of coronary heart disease compared with men with type 2 diabetes, so that the impact of diabetes on the risk of coronary death is significantly greater for women than men [13]. In the present study we were able to confirm this finding and the gender-specific relative difference in the risk of first fatal or non-fatal MI was most clear in the middle age category.

In previous studies, the methods used for classifying depression vary and symptom grading scales or other forms of self-reported data are often used [20]. In our register-based study we only had data on use of antidepressant treatment and not about the severity of depression or mental status.

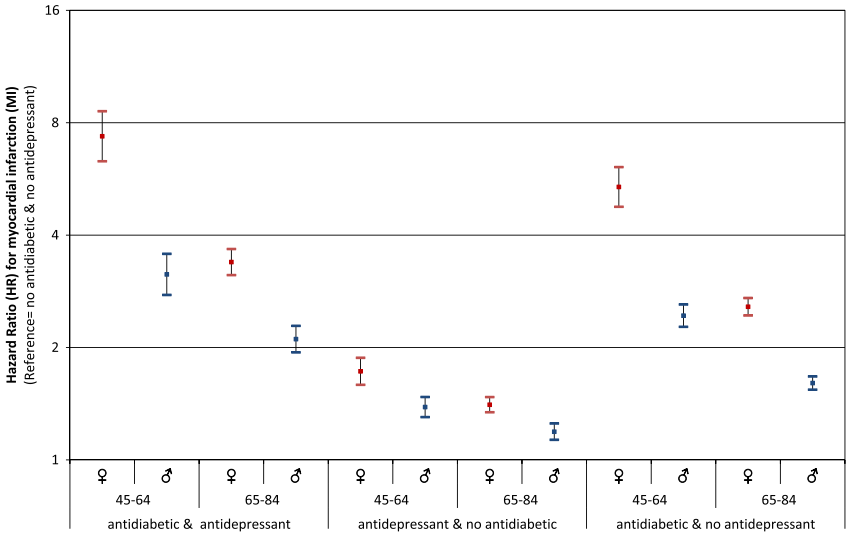

FIGURE 2 Hazard ratios (HRs) for a first myocardial infarction (MI) in participants receiving antidiabetic and/or antidepressant treatment among Swedish residents. HR and 95% CIs for a first MI among men (blue) and women (red) with antidiabetic drugs only, antidepressant drugs only, or antidiabetic and antidepressant drugs combined as markers of disease, compared with the reference; neither antidiabetic nor antidepressant drugs. Subjects are stratified by age: 45–64 and 65–84 years.

Antidepressant drugs have been reported to affect glycaemic control and to trigger the onset of Type 2 diabetes [10,12,21–23]. When considering the risk of diabetes onset after antidepressant therapy it is difficult to differentiate between the possible diabetogenic side effects of antidepressants *per se* (such as weight gain) and the effects associated with the depressive disorder [22,23]. Serotonin reuptake inhibitors have been reported to confer a glucose-lowering effect [12,24] and animal model studies have reported glucose increment from tricyclic antidepressants [25]; however, results from a longitudinal register study over 8 years showed that serotonin reuptake inhibitors and tricyclic antidepressants did not affect glycaemic control [25].

The strengths of the present study include the large study population, which made it possible to stratify data into subgroups and still have statistical power to achieve relatively narrow CIs. A further strength is that the data were population-based, with complete national coverage which reduces possible recall and selection bias. The different registers used have high validity [14] and full coverage of the requested variables. The Myocardial Infarction Statistics register holds information regarding MI diagnosis from all hospital wards and information for re-infarction dating back to 1987, which enabled us to include only subjects with first MI. The Swedish Prescribed Drug Register holds information regarding all dispensed pharmaceuticals, both from public and private prescribing physicians.

The study also has some limitations because of its methodology. First, we had no information regarding the reasons for antidepressant and antidiabetic treatment. The indication for treatment may therefore have been a wide range of conditions, such as neuralgias or anxiety disorders. Anxiety disorders are, however, a very common comorbidity for depression [5]. Metformin is also used as a treatment for polycystic ovary syndrome, but to a very small extent in comparison with diabetes. Second, the study design meant that only one dispensing of antidepressant drugs during the study period qualified a subject to be categorized as having depression and we did not have information regarding any dispensing of antidepressants before the run-in period 2006–2007. As the pharmaceutical dispensing of glucose-lowering medication was used to define the diabetes category, all patients with Type 2 diabetes who were being managed by lifestyle recommendations only were categorized in the reference group. Dispensed drugs rather than diagnosis of diabetes was used as a marker of diabetes because data from the primary healthcare sector are not included in the National Patient Register, but previous studies have shown that 25% of the patients with diabetes are cared for in the primary healthcare sector solely [26]. Misclassification of patients with diabetes who were receiving dietary treatment only in the non-diabetes group would in fact underestimate the increased MI risk for the diabetes population and therefore this limitation was accepted. In addition, oral treatment, mainly with metformin, is generally started early in the course of Type 2 diabetes. Third, we lacked information on important factors such as smoking status, lipids, BMI or other current medications, such as lipid-lowering agents; however, we did have access to data on antihypertensive drugs and adjustment for this medication did not change the results.

In summary, the linkage of nationwide population-based register data on diseases and drugs is useful for numerous analyses and, because of its scale, also provides valid subgroup estimates. We conclude from the present nationwide study with complete coverage that use of both antidiabetic and antidepressant drugs as markers of diabetes and depression combined was associated with a higher risk of MI compared with diabetes or depression alone. Furthermore, middle-aged women with comorbid diabetes and depression seem to be at a substantially higher relative risk for first fatal or non-fatal MI compared with middle-aged men with comorbid diabetes and depression, which to our knowledge has not previously been shown. In addition to what is known from previous studies, our data lend support to the view that diabetes risk factor control is particularly important in patients with diabetes combined with depression to prevent cardiovascular complications. Accordingly, one possible clinical implication is that careful attention should be paid to all patients, and especially women, with comorbid diabetes and depression in order to control cardiovascular risk factors.

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Competing interests

None declared.

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