

Original Research

# Detecting pre-diabetes and the role of the pharmacist

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## ABSTRACT\*

**Objective:** This study aims to use a pharmacoepidemiological approach to study the drug use of patients during the year prior to diabetes diagnosis (i.e. pre-diabetic patients) and control patients. Drug use might reveal cardiovascular, metabolic and/or endocrinological changes and help to identify indicators for active monitoring of Type 2 diabetes mellitus.

**Methods:** A retrospective case-control study compared drug use of patients with a future diagnosis of diabetes (experimental patients) with patients without a diabetes diagnosis (control patients) based on community pharmacy records. An experimental patient had used oral hypoglycaemic drugs during 2005 or 2006. Experimental and control patients were matched in terms of age, gender and quarter of index date. Drugs were selected based on possible comorbidities of diabetes. Drug use was expressed as a binary variable, indicating whether or not a patient took specific drugs. Drug use was compared between experimental patients during the year prior to diagnosis and control patients using the chi-squared test.

**Results:** Our dataset covered 5,064 patients (1,688 experimental and 3,376 control patients). A higher probability of taking cardiovascular drugs was observed for specific subgroups of patients with pre-diabetes as compared to control patients: this trend was observed for men as well as for women, for various cardiovascular drug classes, and for different age groups ( $p < 0.05$ ), although it was not always statistically significant for the 29-38 age group. For each selected age and gender group, patients with pre-diabetes had a higher probability of taking a combination of a lipid-modifying agent and an antihypertensive drug than control patients ( $p < 0.005$ ).

**Conclusions:** Using community pharmacy data, this study demonstrated that age and a characteristic drug use pattern could contribute to detecting pre-diabetes. There is a potential role for community pharmacists to follow up drug indicators

of patients with a view to refer high-risk people for screening by a physician.

**Keywords:** Diabetes Mellitus, Type 2. Diagnosis. Primary Prevention. Drug Utilization. Community Pharmacy Services. Belgium.

## DETECCIÓN DE PRE-DIABETES Y EL PAPEL DEL FARMACÉUTICO

### RESUMEN

**Objetivo:** Este estudio trata de usar un abordaje pharmacoepidemiológico para estudiar el uso de medicamentos durante el año anterior al diagnóstico de diabetes (i.e. pacientes pre-diabéticos) y pacientes control. El uso de medicamentos podría revelar cambios cardiovasculares, metabólicos y/o endocrinos y ayudar a identificar indicadores para la monitorización activa de la diabetes mellitus tipo 2.

**Métodos:** Un estudio caso-control retrospectivo, basado en los historiales de farmacias comunitarias, comparó el uso de medicamentos de pacientes con un diagnóstico futuro de diabetes (pacientes experimentales) con pacientes sin diagnóstico de diabetes (pacientes control). Un paciente experimental había usado medicamentos durante 2005 o 2006. Los pacientes experimentales y controles fueron emparejados en relación a edad, género, trimestre de indexación. Los medicamentos fueron seleccionados en base a las posibles comorbilidades de la diabetes. El uso de medicamentos se expresó como una variable binaria, indicando si el paciente había o no tomado un medicamento específico. Se comparó el uso de medicamentos entre los pacientes experimentales durante el año anterior al diagnóstico y los pacientes control utilizando el test chi cuadrado.

**Resultados:** Nuestro fichero incluyó 5.064 pacientes (1.688 experimentales y 3.376 control). En subgrupos específicos de pacientes con pre-diabetes, se observó una mayor probabilidad de tomar medicamentos cardiovasculares que en los pacientes control: esta tendencia apareció tanto en hombres, como en mujeres, para varios grupos terapéuticos de medicamentos cardiovasculares, y para diferentes grupos etarios ( $p < 0,05$ ), aunque no fue estadísticamente significativo para el grupo de 29-38 años. Para cada grupo seleccionado de edad y género, los pacientes con pre-diabetes tenían una probabilidad mayor de tomar una combinación de anti-hiperlipémico y antihipertensivo que los controles ( $p < 0,005$ ).

**Conclusiones:** Utilizando datos de farmacias comunitarias, este estudio demostró que la edad y un patrón de uso de medicamentos característico

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puede contribuir a detectar pre-diabetes. Existe un papel potencial del farmacéutico siguiendo los indicadores de medicamentos de pacientes con vistas a remitir a los médicos personas de alto riesgo.

**Palabras clave:** Diabetes Mellitus, Tipo 2. Diagnóstico. Prevención Primaria. Utilización de medicamentos. Servicios de farmacias comunitarias. Bélgica.

## INTRODUCTION

Type 2 diabetes mellitus is associated with significant morbidity, impaired quality of life, mortality; and is a primary driver of health care costs and lost productivity.<sup>1,2</sup> This clinical and economic burden is not limited to patients who have diabetes, but may already be imposed on patients prior to diagnosis (so-called pre-diabetes).<sup>3-6</sup> This underlines the importance of prevention of diabetes and health care of pre-diabetes. Indeed, multiple studies have supported the effectiveness of lifestyle interventions and metformin therapy for patients suffering from impaired fasting glucose and/or impaired glucose tolerance, conditions where blood glucose levels are higher than normal but not high enough to be classified as diabetes.<sup>7-9</sup> Previous research has indicated that general practitioners pay little attention to the clinical significance of impaired glucose tolerance and, thus, may fail to diagnose pre-diabetes.<sup>10</sup>

A previous study has demonstrated that community pharmacists can contribute to targeted screening by informing people about Type 2 diabetes mellitus and encouraging high-risk people to visit a physician to be screened.<sup>11</sup> Another way in which community pharmacy may aid screening for diabetes is the analysis of patient drug use. The aim of this study is to use a pharmacoepidemiological approach to comparatively study the pattern of drugs used by patients during the year prior to diabetes diagnosis (i.e. pre-diabetic patients) and control patients. Drug use might reveal cardiovascular, metabolic and/or endocrinological changes and help to identify indicators for active monitoring of Type 2 diabetes mellitus that can be derived from community pharmacy databases. Our study will add specific drugs to a checklist to select high-risk patients and enhance the yield of preventing or postponing the onset of Type 2 diabetes mellitus.

## METHODS

### Data sources

In Belgium, community pharmacies generally transfer data on reimbursed drugs to the reimbursement department of a regional pharmaceutical society. The pharmaceutical society checks these data and then forwards them to the various health insurance funds and ultimately to the National Institute for Health and Disability Insurance, the Belgian third-party payer, for reimbursement purposes. Our study drew on

patient-level data on reimbursed drugs transmitted by 275 community pharmacies in the Belgian province of Limburg to the the Royal Pharmaceutical Society of Limburg ('Koninklijk Limburgs Apothekers Verbond'). In order to comply with privacy rules, data were anonymised by the Royal Pharmaceutical Federation of Limburg. Data from January 2004 to December 2007 were available for this study.

### Study participants

The study enrolled patients with a future diagnosis of diabetes (experimental patients) and patients without a future diagnosis (control patients). A subject was identified as an experimental patient if (s)he was a new user of oral hypoglycaemic drugs such as metformin, sulfonylurea, glinides and glitazones during 2005 or 2006. Metformin may also be prescribed for patients with polycystic ovary syndrome, but this is likely to involve a small number of patients.<sup>4</sup> Furthermore, experimental patients had to take at least two packages of the first oral hypoglycaemic drug during the following year. In this way, patients who sporadically took a hypoglycaemic drug were excluded. The study enrolled patients probably suffering from Type 2 diabetes mellitus by excluding patients diagnosed before 29 years of age or patients taking insulin. Control patients had not used insulin or oral hypoglycaemic drugs during the study period.

For each experimental patient, two control patients were randomly selected from all patients who had never used insulin or oral hypoglycaemic drugs. The community pharmacy database contained data on age and gender of patients (but unfortunately not on other patient characteristics or clinical indicators) and provided a complete overview of the reimbursed drugs used. Therefore, experimental and control patients were matched in terms of five-year age bands, gender and quarter of index date (referring to the date of the first oral hypoglycaemic drug in the experimental group or the analogue date in the control group). The pre-diabetic period was identified as the year preceding the index date and inclusion was restricted to those patients who used at least one reimbursed drug every year throughout the entire study period (2004-2007).

### Study design

A retrospective case-control study compared drug use between experimental patients during the pre-diabetic period and control patients. This design allowed us to investigate whether experimental patients had a higher probability of drug use as compared with control patients.

### Drug use

For each patient, drug use was registered according to the ATC (Anatomical-Therapeutic-Chemical) classification system, which is based on the organ or system on which drugs mainly act and in subcategories according to substance class. ATC groups were selected based on possible comorbidities associated with diabetes as described in the literature.<sup>12-19</sup> Drug use was expressed as a binary variable, with the values '1/0' indicating

whether or not a patient took drugs belonging to a particular drug class.

### Statistical analysis

Drug use was compared between experimental and control patients using the chi-squared test. Data were analysed in SPSS 16.0 for Windows.

### RESULTS

Our dataset covered 5,064 patients, consisting of 1,688 patients with pre-diabetes and 3,376 control patients. Mean age at index date was 57 years. Fifty-two percent of patients were male. The demographic characteristics of the patient sample are described in Table 1.

	Experimental group	Control group
N	1,688	3,376
Age, N (%) <sup>*</sup>		
Mean age	57	57
29-38 years	51 (3%)	102 (3%)
39-48 years	222 (13%)	444 (13%)
49-58 years	634 (38%)	1,268 (38%)
59-68 years	781 (46%)	1,562 (46%)
Gender, N (%) <sup>*</sup>		
Men	886 (52%)	1,772 (52%)
Women	802 (48%)	1,604 (48%)
Quarter of index date		
Jan '05 - March '05	81	162
April '05 - June '05	223	446
July '05 - Sept'05	210	420
Oct '05- Dec '05	275	550
Jan '06 - March '06	303	606
April '06 - June '06	246	492
July '06 - Sept'06	182	364
Oct '06 - Dec '06	168	336
<sup>*</sup> Experimental and control patients were matched in terms of five-year age bands, gender and quarter of index date.		

Table 2 compared the probability of drug use between experimental and control patients. A higher probability of cardiovascular drug use was observed for specific subgroups of patients with pre-diabetes as compared to control patients. This trend was observed for men as well as for women and for different age groups ( $p < 0.05$ ), although it was not always statistically significant for the 29-38 age group. This applied to C03 diuretics, C07 beta-blocking agents, C08 calcium channel blockers, C09 agents acting on the renin-angiotensin system or C10 lipid-modifying agents. The probability of using A02 drugs for acid-related disorders, N06A antidepressants or R03 drugs for obstructive airway diseases did not vary between experimental and control groups selected by age and gender, except for elderly women.

With a view to developing a checklist of specific drugs to select patients for active monitoring, the analysis focused on patients taking a lipid-modifying agent in combination with an antihypertensive drug (beta-blocking agent, calcium channel blocker, agent acting on the renin-angiotensin system). Figure 1 shows that, for each selected age and gender group, patients with pre-diabetes had a higher probability of taking a combination of a lipid-modifying agent and an antihypertensive drug than control patients ( $p < 0.005$ ).

Patient group (years old)	Pre-diabetic (n=1,688) <sup>*</sup>	Control (n=3,376) <sup>*</sup>	P-value
<b>A02 Acid-related disorders</b>			
29-38 men	17%	26%	0.420
39-48 men	23%	19%	0.347
49-58 men	16%	17%	0.603
59-68 men	23%	21%	0.449
29-38 women	18%	16%	0.836
39-48 women	25%	17%	0.109
49-58 women	26%	15%	<0.001
59-68 women	28%	19%	0.001
<b>C03 Diuretics</b>			
29-38 men	9%	0%	0.042
39-48 men	9%	1%	<0.001
49-58 men	10%	4%	<0.001
59-68 men	21%	9%	<0.001
29-38 women	14%	2%	0.022
39-48 women	12%	2%	<0.001
49-58 women	21%	7%	<0.001
59-68 women	34%	13%	<0.001
<b>C07 Beta-blocking agents</b>			
29-38 men	43%	11%	0.002
39-48 men	30%	13%	<0.001
49-58 men	40%	20%	<0.001
59-68 men	50%	29%	<0.001
29-38 women	14%	4%	0.072
39-48 women	38%	14%	<0.001
49-58 women	50%	21%	<0.001
59-68 women	57%	34%	<0.001
<b>C08 Calcium channel blockers</b>			
29-38 men	13%	4%	0.189
39-48 men	9%	2%	0.005
49-58 men	14%	6%	<0.001
59-68 men	18%	13%	0.023
29-38 women	0%	2%	0.477
39-48 women	6%	1%	0.031
49-58 women	11%	4%	<0.001
59-68 women	16%	8%	<0.001
<b>C09 Agents acting on the renin-angiotensin system</b>			
29-38 men	17%	4%	0.070
39-48 men	17%	5%	<0.001
49-58 men	26%	14%	<0.001
59-68 men	35%	22%	<0.001
29-38 women	11%	0%	0.013
39-48 women	17%	5%	0.001
49-58 women	22%	10%	<0.001
59-68 women	37%	16%	<0.001
<b>C10 Lipid-modifying agents</b>			
29-38 men	9%	4%	0.466
39-48 men	27%	15%	0.006
49-58 men	38%	24%	<0.001
59-68 men	44%	31%	<0.001
29-38 women	7%	0%	0.043
39-48 women	17%	5%	<0.001
49-58 women	27%	13%	<0.001
59-68 women	41%	27%	<0.001
<b>N06A Antidepressants</b>			
29-38 men	26%	13%	0.178
39-48 men	16%	10%	0.163
49-58 men	17%	12%	0.053
59-68 men	13%	9%	0.078
29-38 women	21%	20%	0.848
39-48 women	25%	18%	0.201
49-58 women	23%	19%	0.099
59-68 women	24%	19%	0.040
<b>R03 Drugs for obstructive airway diseases</b>			
29-38 men	9%	2%	0.210
39-48 men	9%	6%	0.286
49-58 men	7%	6%	0.662
59-68 men	10%	7%	0.051
29-38 women	11%	7%	0.577
39-48 women	8%	4%	0.147
49-58 women	10%	6%	0.014
59-68 women	8%	7%	0.471

<sup>\*</sup> Percentage of patients taking drugs.

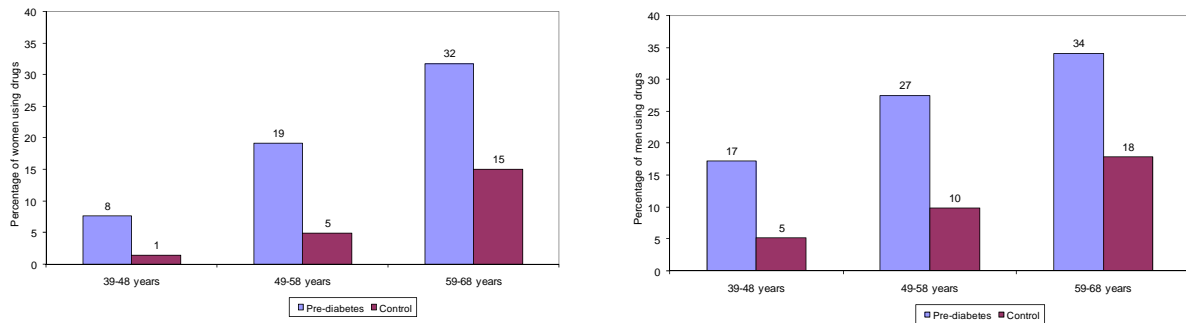


Figure 1. Combined cardiovascular drug use in pre-diabetes and control patients. Patients took a lipid-modifying agent in combination with an antihypertensive drug (beta-blocking agent, calcium channel blocker, agent acting on the renin-angiotensin system).

## DISCUSSION

This study showed that during the year prior to diabetes diagnosis, patients had a higher probability of taking one or multiple cardiovascular drugs as compared to control patients. This association is to be expected given that patients with an increased cardiovascular risk are also at a higher risk of developing diabetes.<sup>20</sup> In particular, the combination of a lipid-modifying agent and an antihypertensive drug (beta-blocking agent, calcium channel blocker, agent acting on the renin-angiotensin system) needs to be added to a checklist to identify high-risk people. This observation applied to men and to women and across most age groups. The study points to the potential role for community pharmacists to follow up drug indicators for active monitoring and prevention of Type 2 diabetes and eventually to encourage high-risk people to visit a physician to be screened. An economic evaluation assessing the cost-effectiveness of such a community pharmacy intervention is called for.

This observational, retrospective study has made use of a dataset on prescription drugs in community practice. It indicates that community pharmacy databases can be accessed by pharmacists to follow up drug indicators of specific patient groups. This dataset reflected actual clinical practice in the community. However, it should be noted that no data were available on over-the-counter drugs or drugs that are not reimbursed by the Belgian third-party payer. Similar datasets exist in other European countries and have, until now, remained a largely untapped resource in this kind of research.

The reader should be aware of the characteristics of our study sample, particularly the fact that the community pharmacy records did not contain clinical data. Experimental patients were identified by their use of oral hypoglycaemic drugs such as metformin, sulfonylurea, glinides and glitazones. However, our sample of experimental patients may have included patients with impaired fasting glucose and/or impaired glucose tolerance who are treated with metformin without ever developing diabetes. Also, diabetic patients who started on diet alone and later moved on to oral therapy may have been included mistakenly as experimental patients. Since the sample enrolled patients who used at least one prescription drug per year, the control group may have higher morbidity than the Belgian population

that does not take drugs. As a higher probability of drug use was observed when comparing pre-diabetic patients with a control group of patients who take drugs, we would expect this result to be corroborated when comparing pre-diabetic patients with a healthy control group.

Data used in this study suffered from a number of limitations. Drug use was expressed as a binary variable, indicating whether or not a patient took drugs. A more accurate indicator would have been to measure drug use in defined daily doses. Also, the analysis did not consider the duration of drug use and did not take into account the fact that not all drugs dispensed to patients are actually taken by patients. Finally, the community pharmacy database contained few data about demographic characteristics of patients. Future studies need to explore whether the association between drug use and pre-diabetes is influenced by other demographic or socio-economic variables.

Drug use might reveal cardiovascular, metabolic and/or endocrinological changes and, therefore, our findings encourage the use of a pharmaco-epidemiological approach to comparatively study the pattern of drug use between diabetic patients during the years prior to diagnosis and controls. There is also a need for further investigation on the process preceding the diagnosis of Type 2 diabetes mellitus. For instance, the higher use of beta-blocking agents by experimental patients may derive from the fact that beta-blocking agents can cause an increase in fasting blood glucose and impaired glucose tolerance.<sup>21</sup>

## CONCLUSIONS

Using community pharmacy data, this study demonstrated that during the year prior to diabetes diagnosis, patients had a higher probability of using a combination of a lipid-modifying agent and an antihypertensive drug than control patients. There is a potential role for community pharmacists to follow up drug indicators of patients with a view to identify and refer high-risk people for screening by a physician.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this manuscript. No financial support was received for this study.

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