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**Prevalence and detection rate of underlying disease in  
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Kingdom: A retrospective database study**

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**Prevalence and detection rate of underlying disease in men with erectile dysfunction receiving phosphodiesterase type 5 inhibitors in the United Kingdom: A retrospective database study**

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 Manuscripts

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4 **Prevalence and detection rate of underlying disease in men with**  
5 **erectile dysfunction receiving phosphodiesterase type 5 inhibitors**  
6 **in the United Kingdom: A retrospective database study**  
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11 **Kirby MG<sup>1</sup>, Schnetzler G<sup>2</sup>, Zou KH<sup>3</sup>, Symonds T<sup>4</sup>**

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29 30 31 32	<b>Running header</b>	Detection of underlying disease in men prescribed a PDE5i
33 34 35 36 37 38	<b>Key words</b>	Erectile dysfunction, phosphodiesterase type 5 inhibitors, underlying disease, prevalence, cumulative incidence, clinical assessment, THIN database, disease detection
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## ABSTRACT

**Aim:** To determine the rate of newly detected underlying disease in men receiving their first (index) phosphodiesterase type 5 inhibitor (PDE5i) prescription.

**Methods:** This non-interventional, retrospective study used anonymised patient records from UK general practices identified from the THIN database. Records of men aged  $\geq 18$  years who received an index PDE5i prescription between January 1999 and June 2008 and with a continuous medical history ( $\geq 60$  months) before the index prescription were included. Primary endpoints were the prevalence of underlying disease prior to the index prescription and the detection rate as cumulative incidence of such a diagnosis in the 3 months following the index prescription. Assessments included comparison with age-matched controls, comparison with identical time periods immediately before, and one year after, index prescription, and changes over time during the study period. Descriptive statistics, analysis of proportions and multivariate logistic regression analysis were used.

**Results:** Among the 24,708 patients receiving a PDE5i, the prevalence of any underlying diagnosis before the index prescription was 70.23%; prevalence of vasculogenic disease was highest (48.20%). The detection rate of any underlying disease was 11.53%, and again highest for vasculogenic disease (4.07%). Compared with an age-matched control population, the additional detection rate of an unknown underlying disease at PDE5i prescription was 45 for hypertension, 61 for hypercholesterolaemia, 38 for diabetes and 5 for hypogonadism per 10,000 men.

**Conclusion:** Only a minority of men with [erectile dysfunction](#) have a previously undiagnosed important underlying disease that is uncovered at the time of an initial PDE5i prescription by a GP.

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**Word count:** [251](#) (including section headings)

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3 ***What is already known about this topic?***  
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5 ED can be caused by a variety of potentially underlying and reversible factors. Recently, ED  
6 has been identified as an independent risk factor for CVD, including angina, myocardial  
7 infarction, stroke and transient ischaemic attack. Management recommendations for ED  
8 suggest a clinical assessment to detect underlying conditions when prescribing a PDE5i.  
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11 ***What does this article add?***  
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13 These findings suggest that most men with ED have known comorbidities, identified during  
14 routine healthcare assessments and not in the context of a PDE5i prescription. However it  
15 may be beneficial that men are regularly asked about erection problems in clinical practice,  
16 as the opportunistic identification of ED can be a trigger to address CVD risk factors more  
17 effectively, enabling the targets of the UK Quality and Outcomes Framework to be achieved.  
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## INTRODUCTION

Erectile dysfunction (ED), defined as the inability to attain and/or maintain an erection sufficient for satisfactory sexual intercourse, is a prevalent medical condition affecting approximately 10–50% of the male population aged over 40 years (1–4). The origin of ED can be physical (organic ED), psychological or a combination of the two, and the condition is influenced by vasculogenic (including cardiovascular disease [CVD]), neurogenic, anatomical/structural, hormonal (e.g. hypogonadism), drug-induced, and psychogenic factors (5,6).

Since the launch of the first oral phosphodiesterase type 5 inhibitor (PDE5i) sildenafil more than a decade ago (7), PDE5is have become the first-line therapeutic option for the treatment of ED due to their established efficacy and favourable safety profile (8–10). ED has recently been identified as an independent risk factor for CVD, including angina, myocardial infarction, stroke and transient ischaemic attack. In an analysis of data from more than 9,000 men aged 55 years or older enrolled in the Prostate Cancer Prevention Trial, men with ED were reported to have an approximate twofold increased risk of CVD compared with men without ED (11). Furthermore, ED has been reported to precede a major cardiovascular event by an average of about five years (12). These findings may be explained by the artery size hypothesis. [Penile arteries are smaller than coronary arteries \(1–2 mm vs 3–4 mm\), potentially explaining why ED presents in advance of coronary artery disease \(CAD\) symptoms: as a similar degree of endothelial dysfunction may be subclinical in the larger vessels. This could further explain](#) the high frequency of ED symptoms observed in patients with CAD, and the lack of concomitant symptoms of CAD observed in most patients with ED (13). Additionally, current evidence suggests that organic ED and CAD share a common aetiology in endothelial dysfunction (14–16).

Based on the variety of potentially underlying and reversible factors leading to ED, and the strong association between ED and the subsequent development of clinical cardiovascular events, both international (9,10,17) and UK-based (8) treatment guidelines recommend a targeted medical and psychosexual assessment of ED (including cardiovascular risk factors) prior to treatment with a PDE5i. However, despite the known burden and extent of comorbid conditions in patients with ED (18), data on the detection rate of underlying medical conditions in men assessed for the treatment of ED are limited to specialist single-centre studies (19,20). So far, no study has assessed the detection rate for previously unknown

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2 underlying medical conditions in men with ED undergoing medical evaluation for a PDE5i  
3 prescription in general practice in the UK.  
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5 The aim of this study was to determine the outcome of diagnostic activities performed in the  
6 temporal context of a PDE5i prescription by assessing the detection rate of newly diagnosed  
7 medical conditions following the initial prescription. Several analyses were conducted to  
8 account for potential influencing factors including the known difference in prevalence rates  
9 for cardiovascular risk factors in the ED population compared with a male population who  
10 had not previously received a PDE5i prescription, and the diagnostic assessments prior to  
11 and post prescription. Differences in diagnostic activities performed at the time when PDE5is  
12 were introduced (in the late nineties) and in more recent years (when ED became  
13 recognised as a potential harbinger for CVD) were also investigated.  
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## 18 19 **METHODS**

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21 This was a non-interventional, retrospective database study of medical records registered in  
22 The Health Improvement Network (THIN) database in the UK ([www.thin-uk.com](http://www.thin-uk.com)), a primary-  
23 care administrative database containing the electronic medical records of 5% of the UK  
24 population from the clinical systems of over 385 GP practices. As a managed database,  
25 records undergo systematic quality assessments. This database has previously been  
26 validated for epidemiological research (21) and has recently been used for epidemiological  
27 research in the field of urology (22–24). The THIN Data Collection Scheme was approved by  
28 the South-East Multicentre Research Ethics Committee (SE-MREC) in the UK. This study  
29 protocol was approved by the independent scientific review committee of THIN.  
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34 The primary objectives of the study were to determine the prevalence of underlying disease  
35 in male patients prior to receiving a first (index) PDE5i prescription, to establish the detection  
36 rate of new diagnoses (defined as the cumulative incidence of such a diagnosis in the 3  
37 months [day 0 to day 91] following the index prescription), and to determine the role of ED  
38 assessment in the identification of underlying disease in men receiving their first PDE5i  
39 prescription. The diagnoses of interest investigated in this study were adapted from the  
40 diagnostic evaluations recommended in the European Urology Association Guidelines on  
41 Male Sexual Dysfunction (9,25) and were divided into a vasculogenic, neurogenic,  
42 anatomic/structural, hormonal, pharmacologic (drug prescribed <1 year before index  
43 prescription) and psychogenic category (Table 1). In addition, diagnoses of hypertension,  
44 hypercholesterolaemia, diabetes and hypogonadism were specifically assessed. The PDE5i  
45 prescription index date was used as a surrogate parameter for the time when a complete  
46 medical check would have been indicated. The 3-month time period following the index  
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2 prescription was considered sufficient to include any new diagnosis identified based on  
3 additional tests requested at the time of PDE5i prescription. In order to fully capture the  
4 prevalence of underlying diseases, only patients with a continuous medical history of  $\geq 60$   
5 months prior to the index prescription were included in the study.  
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8 Secondary study objectives included comparison of the prevalence and detection rate of  
9 underlying disease identified in the study subjects at index prescription with an age-matched  
10 control population not receiving a PDE5i. In addition, the detection rate of new diagnoses at  
11 index prescription was compared with that in a 3-month period immediately before the index  
12 PDE5i prescription (day -92 to day -1) and a 3-month period one year after the index  
13 prescription (day 366 to day 457) in patients with a continuous medical history of  $\geq 457$  days  
14 following their index prescription (target sub-group population) to assess the detection of  
15 underlying conditions pre- and post PDE5i prescription. Finally, temporal trends were  
16 analysed among the target population by comparing the prevalence and 3-month post index  
17 detection rate of underlying medical conditions in subjects with an index prescription  
18 between January 1<sup>st</sup>, 1999 and December 31<sup>st</sup>, 2001 with that in subjects with a more recent  
19 index prescription (between July 1<sup>st</sup>, 2006 and June 30<sup>th</sup>, 2008). This was done to see if the  
20 increased awareness of ED as a marker of underlying disease had made any impact on the  
21 detection rate.  
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### 28 ***Patient population***

29 Study participants were identified from anonymised THIN patient records. Records of  
30 acceptable quality (THIN patflag "A" and "C") of men aged  $\geq 18$  years who received an index  
31 PDE5i prescription (sildenafil, tadalafil or vardenafil) between January 1<sup>st</sup>, 1999 and June  
32 30<sup>th</sup>, 2008 were identified from the database (target population). Men not meeting these  
33 criteria and females were excluded.  
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36 A reference population of age-matched controls was identified from the database (control  
37 population). The same inclusion criteria applied with the exception of a PDE5i prescription  
38 during the study period. For each subject of the target population, three control subjects  
39 were randomly selected based on the age at the first data entry date in any given year, and  
40 strata were filled starting at the end of the study period and working backwards (towards  
41 1999).  
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### 45 ***Data collection and study endpoints***

46 The relevant READ codes for all diagnoses and Multilex drug codes for the pharmacological  
47 compounds were used to search the records of study participants and age-matched controls  
48 for instances of diagnoses of the medical conditions detailed in Table 1. To avoid multiplicity,  
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only one code per diagnosis was captured, and the presence of at least one diagnosis defined whether a disease of a given category was present. All ever-coded diagnoses during the 60 months prior to the first PDE5i prescription (or date used for matching of control patients) were used to define the prevalence of underlying medical conditions at the time of index prescription. The cumulative incidence, i.e. the proportion of new diagnoses of interest within the 3-month period (0–91 days) following the index PDE5i prescription (or date used for matching controls) in each population was used to define the detection rate.

### Statistical analysis

Categorical data were reported as counts and proportions, whereas continuous data were reported using descriptive statistics (mean, standard deviation). For the three age-matched controls per study participant, an average of the proportion or value was computed.

Comparisons of the detection rates between groups were made using the difference in proportions for categorical data and the difference in the means for continuous data, along with 95% confidence intervals (CI). For inferential analysis based on large samples, the Chi-square test was used to compare categorical data for the groups of interest. The analysis of proportions and the two-sample t-test were performed to compare the overall mean prevalence, detection rates and the mean age at which men received a new diagnosis for the study participants and the control population. A two-sided p-value of  $<0.05$  was considered statistically significant.

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For study subjects who died after their index prescription date or reference index date (day 0), the last observation carried forward imputation method was used i.e. all observations (diagnostic codes) between day 0 and the date of death were carried forward and defined as a new diagnosis during the time period from day 0 until day 91.

To adjust for potential confounding effects on the difference in incidence of new diagnoses between the target and control populations, a multivariate regression analysis was performed using cardiovascular risk factors (hypertension, diabetes, hypercholesterolaemia, smoking and obesity [body mass index  $>30$ ]) and year of inclusion in the study cohort as covariates.

All statistical analyses were conducted using SAS 9.1 and 9.2 of the SAS Institute Inc., Cary, NC ([www.sas.com](http://www.sas.com)).

## RESULTS

A total of 89,781 men who received an index PDE5i prescription between January 1<sup>st</sup>, 1999 and June 30<sup>th</sup>, 2008 were identified from the THIN database. Among these patients, 24,708

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2 met the inclusion criteria and were included in the target population. A total of 24,479 men in  
3 the target population had a continuous medical history of  $\geq 457$  days and were included in  
4 the subgroup target population. The control group comprised 74,124 male patients. The  
5 baseline characteristics of the target population and control group are summarised in  
6 Table 2.  
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### 10 ***Prevalence of existing diagnoses***

11 The prevalence of any coded diagnosis before the index PDE5i prescription was 70.23%  
12 (95% CI: 69.66–70.80). When each specific diagnosis was considered, vasculogenic  
13 diagnoses and co-medication (pharmacologic category) were found to have the highest  
14 prevalence rates of 48.20% (95% CI: 47.58–48.83) and 42.97% (95% CI: 42.36–43.59),  
15 respectively. The prevalence of all other categories was low (<10%). The most prevalent  
16 vasculogenic diagnoses were hypertension 19.93% (95% CI: 19.43–20.43), diabetes 9.69%  
17 (95% CI: 9.32–10.06) and hypercholesterolaemia 8.26% (95% CI: 7.92–8.61).  
18 Hypogonadism was present in 0.19% (95% CI: 0.17–0.25) of the men prior to receiving a  
19 PDE5i. [Figure 1]  
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### 24 ***Incidence of new diagnoses***

25 The detection rate of any previously unknown underlying condition in the 3 months following  
26 the index PDE5i prescription was 11.53% (95% CI: 11.13–11.93). The detection rate of a  
27 vasculogenic diagnosis was 4.07% (95% CI: 3.82–4.32), including new detection of  
28 hypertension, hypercholesterolemia or diabetes in 1.21% (95% CI: 1.07–1.34), 1.04% (95%  
29 CI: 0.92–1.17) and 0.69% (95% CI: 0.59–0.80) of men, respectively [Table 3].  
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### 34 ***Comparison versus an age-matched control population***

35 Compared with the control population, the target population had a significantly higher  
36 prevalence of existing diagnoses overall (70.23% vs 55.73%;  $p < 0.001$ ) and in each category  
37 [Figure 1]. The detection rate of new diagnoses overall was also significantly higher in the  
38 target population compared with the control population (11.53% vs 7.49%;  $p < 0.001$ ), and  
39 similar findings were seen when each specific category or diagnosis was considered. The  
40 absolute difference between the detection rates was calculated and shown in Table 3. [The  
41 mean age of men who received a new diagnosis of diabetes or urologic, neurogenic,  
42 hormonal, or psychogenic ED in the three months post-prescription was significantly lower in  
43 the target population compared with the age-matched controls \(Table 4\). No significant  
44 difference was found for vasculogenic diagnoses or hypogonadism.](#)  
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### ***Adjustment for potential confounders***

Table 3 summarises the odds ratio based on multivariate logistic regression analysis for the detection of a new diagnosis after adjustment for pre-existing cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes, smoking and obesity) and the year of inclusion in the study cohort. Odds ratios remained statistically significant for all diagnostic categories, except for vasculogenic disease.

### ***Comparison of detection rate to a 3-month period prior to the index date and a 3-month period one year after the index date***

The detection rates in the 3 month period prior to index prescription (day -92 to -1), and the 3 month period 1 year after prescription (day 366 to 457), were both lower than that in the 3 months post-index prescription for all diagnoses except for the urologic diagnoses and diabetes (which were diagnosed with a significantly higher frequency in the 3 months prior to index prescription) [Figure 2]. While the detection rate for any new diagnosis immediately prior to the prescription was not statistically different to that in the 3 months post-index prescription (11.08% vs 11.49%;  $p=0.153$ ), it was significantly lower one year later when compared to the time of prescription (5.65% vs 11.49%;  $p<0.001$ ).

### ***Change of prevalence and detection rate of underlying conditions over time***

Prevalence of any underlying condition was significantly lower in the population receiving a PDE5i in the early study period included in 1999 and 2001 ( $n=892$ ) compared with the population included between mid 2006 and mid 2008 ( $n=9,862$ ), the end of the study period (67.49% vs 72.14%;  $p=0.004$ ). The proportion of men with vasculogenic disease (44.39% vs 54.66%;  $p<0.001$ ) or co-medication (43.50% vs 48.74%;  $p=0.003$ ) at index prescription was significantly lower in the early study population, whereas the prevalence of psychogenic conditions (12.33% vs 8.27%;  $p<0.001$ ) was significantly higher, compared with the later period. However, detection rates overall (11.32% vs 11.06%;  $p=0.813$ ), and for each category, were not statistically different over time [Figure 3].

## **DISCUSSION**

This retrospective database study using records from THIN found that seven out of ten men have an established diagnosis of underlying disease before they receive their first PDE5i prescription. The most common underlying medical conditions were vasculogenic diagnoses and co-medication, with prevalence rates of 48% and 43%, respectively. As expected, the prevalence of underlying disease (all medical conditions combined and considered separately) which could potentially lead to ED was significantly higher among patients

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2 receiving a PDE5i prescription compared with the reference population of age-matched  
3 controls with no PDE5i prescription. Similarly, the detection rate of conditions potentially  
4 underlying ED was statistically significantly higher compared with the detection rate of a  
5 control population (11.5% vs 7.5% for any diagnosis).  
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8 The outcome of diagnostic activities recommended for the assessment of ED at a PDE5i  
9 prescription was further assessed using the absolute differences in detection rates between  
10 the target and the control population. The study results suggest that following clinical  
11 assessment for ED, the absolute number of newly detected underlying diagnoses (per  
12 10,000 men) above the normal detection rate is 45 for hypertension, 61 for  
13 hypercholesterolemia, and 38 for diabetes. Furthermore, previously undiagnosed  
14 hypogonadism was detected in an additional 5 out of 10,000 men assessed for an initial  
15 PDE5i prescription. The odds ratios remained statistically significant for subjects in the target  
16 group versus the control group, even when adjusted for potential confounding factors in the  
17 ED population (resulting from a higher prevalence of pre-existing CV risk factors) and the  
18 skewed inclusion date of the control population (towards the end of the study period), with  
19 the exception of new vasculogenic diagnosis where the odds ratio suggested no difference  
20 when adjusted for pre-existing CV risk factors. These findings imply that only a relatively  
21 small number of men with ED will have a previously undiagnosed, important underlying  
22 disease uncovered at the time of an initial PDE5i prescription. However, it may remain  
23 beneficial that men are regularly asked about erection problems in clinical practice, given  
24 that a substantial proportion of men with ED do not seek medical advice or treatment (26,27)  
25 or access treatment from sources outside of the healthcare system (28). The opportunistic  
26 identification can be a trigger to assess and manage ED according to accepted treatment  
27 recommendations (8–10), and to address CVD risk factors more effectively, enabling the  
28 targets of the UK Quality and Outcomes Framework (QOF) to be achieved.  
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37 The detection rates reported in this study are similar or somewhat lower than those  
38 described in two single-centre studies. Hatzichristou *et al.* reported that blood tests identified  
39 a previously undiagnosed medical condition in 6.2% of 1,276 evaluable patients with ED  
40 (mean duration 4.9 years) (19). Diabetes mellitus and abnormal lipid profiles were newly  
41 detected in 11 (0.9%) and 37 (2.9%) patients, respectively, and hypogonadism and  
42 hyperprolactinaemia were uncovered in 22 (1.7%) and 8 (0.6%) patients, respectively. In 28  
43 patients (2.2%), a previously unknown urinary tract disease was diagnosed, and in 8 patients  
44 (0.6%) tests revealed a previously unknown neurologic disorder. Solomon *et al.* described  
45 even higher rates following an assessment of 174 subjects in a joint urologic and cardiologic  
46 referral practice using the Princeton Consensus Guideline. The detection rate of  
47 vasculogenic conditions was high, with a new diagnosis of hyperlipidaemia, hypertension or  
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2 diabetes, and suspected significant angina reported in 26%, 10% and 6% of men,  
3 respectively (20). Additionally, a potential urologic disorder was identified in five men and  
4 hyperprolactinaemia was reported in one man.

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6 The overall mean age of the target population of men at the time of their first index  
7 prescription for PDE5i in this analysis of general population data was 59 years. For some  
8 diagnoses, the mean age of men in the target group in the period three months post-  
9 prescription was significantly lower than that in the control population. As this study was not  
10 specifically intended to investigate the age at which these diagnoses were made, it remains  
11 questionable whether ED assessment in the context of a PDE5i prescription currently would  
12 lead to an earlier detection of some potentially underlying conditions.  
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16 Two factors may have contributed to the lower diagnosis rates reported in this retrospective  
17 database study compared with the two specialist single-centre studies. First, patients who  
18 complained about ED might have received a PDE5i prescription only after all the results of  
19 the clinical assessments were available, although guidelines do not explicitly recommend a  
20 deferred treatment. Interestingly, a considerable number of new diagnoses were made in the  
21 3 months prior to the PDE5i prescription, and were substantially lower in the period one year  
22 after the index prescription. The detection rate seen in this later period is within a similar  
23 range to the rate seen in an age-matched control population without a PDE5i prescription.  
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27 A second factor which may account for the lower detection rates reported in this  
28 observational study, compared with previous studies from specialist centres which  
29 specifically investigated the presence of underlying conditions, is the extent to which these  
30 investigations are actually performed by physicians in general practice. Although no  
31 information on this is available from general practitioners, a survey among urologists  
32 suggests these investigations are often abbreviated or deferred: Of 1,590 participating  
33 delegates of the annual congress of the European Association of Urologists 2008, 33%  
34 reported that they would perform further interviews, with 19%, 15% and 7%, respectively,  
35 reporting that they would assess cardiovascular risk factors, order laboratory tests and  
36 perform blood pressure measurements in a man presenting with ED (29). It is difficult to  
37 assess the level of clinical investigation performed during routine GP practice; however, the  
38 comparable detection rates of underlying conditions during the early phase and the later  
39 phase of the study suggest that there was no change over time, despite the statistically  
40 higher prevalence of known vasculogenic diagnoses and co-medication in the cohort  
41 receiving a PDE5i between July 2006 and June 2008. The 2004 UK QOF targets would  
42 likely have contributed to this finding (30).  
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46 This study has limitations inherent to any retrospective database study (31), including the  
47 potential effect that under- and misreporting would have on prevalence and detection rates.  
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2 Further limitations of this study include the fact that the data represent a temporal rather than  
3 a causal relationship between the detection rate of new diagnoses and the PDE5i  
4 prescription. [Furthermore, it can not be ruled out that some men in the control population](#)  
5 [may have had ED \(diagnosed or undiagnosed\) but did not receive treatment.](#) Current  
6 knowledge of the pharmacologic effect and the safety of PDE5i does not support an  
7 inversion of the interpretation, i.e. that hypertension or diabetes is induced by a PDE5i  
8 prescription (17,32,33). More importantly, it is impossible to determine in this study, whether  
9 the symptoms of ED were the cause of the GP visit, or whether ED was identified as part of  
10 other health-related assessments. This could lead to an overestimation of the detection rates  
11 for underlying conditions. Alternatively, and as discussed above, the presented detection  
12 rates could be lower than in reality, since the PDE5i prescription index date was used as a  
13 surrogate parameter for the time when a complete medical check would be performed. This  
14 excludes the detection of underlying conditions diagnosed before the PDE5i was actually  
15 prescribed. Finally, patients with private PDE5i prescriptions were not included in the  
16 analysis and the impact of this on the study outcome remains unknown.  
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## 23 CONCLUSION

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26 The high prevalence and low detection rates observed in this study suggest that in current  
27 clinical practice many of the diagnoses associated with ED, including vasculogenic  
28 conditions are identified during routine healthcare assessments and not as a result of a  
29 diagnostic work-up for ED. As a consequence, the vast majority of men with ED have a  
30 previously known medical condition when asking for a PDE5i treatment. Routine clinical  
31 assessments in the context of a PDE5i prescription appear to uncover an additional case of  
32 hypertension, hypercholesterolaemia or diabetes in approximately one out of 200 men and a  
33 hypogonadism in one out of 2000 men compared with the normal detection rate in an age-  
34 matched control population. No change was seen in the detection rate over the past 10  
35 years.  
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42  
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4 Design of the study: MK, GS, KHZ, TS

5 Analysis of the data: GS, KHZ

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7 Drafting of the manuscript and review for content: MK, GS, KHZ, TS

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**Table 1:** Categories of conditions potentially leading to ED (adapted from the European Urology Association Guidelines)(9,25)

Category	Subcategory	Medical diagnoses
Vasculogenic	Cardiovascular disease	Atherosclerosis
		Ischaemic vascular disease
		Ischaemic heart disease
	Cardiovascular risk factors	Renal failure
		Hypertension
		Diabetes
Hypercholesterolaemia		
Urologic	Anatomical	Smoking
		Obesity
	Iatrogenic	Peyronie's disease
		Hypospadias
Neurogenic	Central	BPH/LUTS
		Prostatectomy (NSRP, TURP)
		Pelvic and retroperitoneal surgery/radiotherapy
	Peripheral	Multiple sclerosis
Hormonal	Central	Multiple system atrophy
		Parkinson's disease
		Spinal cord injury
		Polyneuropathy
Pharmacologic <sup>a</sup>	Peripheral	Hypogonadism (primary/secondary), including hypopituitarism
		Hyperprolactinaemia
		Thyroid disease
		Cushing's and Addison's disease
Psychogenic	Pharmacologic <sup>a</sup>	Thiazides, spironolactone, calcium channel blockers, ACE-inhibitors, beta-blockers, SSRI, tricyclic antidepressants, lithium, MAO inhibitors, benzodiazepines, ranitidine, cimetidine, methotrexate, interferon-alpha, alcohol, cocaine
		Anxiety
		Dementia
		Depression
		Neurotic disorders
		Psychosis
Schizophrenia	Psychogenic	Schizophrenia

ACE, angiotensin-converting enzyme; BPH, benign prostatic hypertrophy; LUTS, lower urinary tract symptoms; MAO, monoamine oxidase; NSRP, nerve-sparing radical prostatectomy; SSRI, selective serotonin reuptake inhibitor; TURP, transurethral resection of the prostate

<sup>a</sup>Drug must have been given in the year prior to initial PDE5i prescription/reference index date

**Table 2.** Baseline characteristics of the study and control populations

	Target population (n=24,708)	Control population (n=74,124)
Age (years)		
Mean (SD)	57.63 (11.59)	57.63 (11.59)
Median (range)	59.0 (18.0–91.0)	59.0 (18.0–91.0)
Weight (kg)		
Mean (SD)	87.95 (16.08)	86.72 (16.82)
Median (range)	86.0 (44.0–200.0)	85.0 (40.0–199.4)
BMI (kg/m <sup>2</sup> )		
Mean (SD)	28.28 (4.56)	28.05 (4.80)
Median (range)	27.7 (14.3–48.0)	27.5 (14.0–48.0)

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- Deleted: 0.8
- Deleted: 220.0

BMI, body mass index; SD, standard deviation.

Smoking was excluded as data on this was not routinely recorded until QOF commenced in 2005. [If weight and BMI values were outside of pre-defined ranges \(<40 to >200 kg and <14 to >48 kg/m<sup>2</sup>, respectively\) they were considered missing.](#)

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**Table 3.** Detection rate of underlying conditions (over three months) in men receiving a PDE5i prescription (target population) and in age-matched controls (control population).

Category or diagnosis	Detection rate, % 95% CI)			Absolute difference in detection rate (%) <sup>a</sup>	Multivariate analysis	
	Target population (n=24,708)	Control population (n=74,124)	p-value		Odds ratio <sup>b</sup> (95% CI)	p-value
Vasculogenic	4.07 (3.82–4.32)	2.89 (2.77–3.01)	<0.001	1.18 (1.46–0.90)	0.96 (0.77–1.18)	0.67897
Hypertension <sup>c</sup>	1.21 (1.07–1.34)	0.76 (0.70–0.82)	<0.001	0.45 (0.29–0.60)	1.81 (1.49–2.19)	<.00001
Hypercholesterolaemia <sup>c</sup>	1.04 (0.92–1.17)	0.43 (0.39–0.48)	<0.001	0.61 (0.47–0.75)	3.45 (2.74–4.34)	<.00001
Diabetes <sup>c</sup>	0.69 (0.59–0.80)	0.31 (0.27–0.35)	<0.001	0.38 (0.12–0.65)	2.83 (2.15–3.72)	<.00001
Urologic	0.45 (0.36–0.53)	0.22 (0.19–0.25)	<0.001	0.23 (0.32–0.13)	2.72 (2.01–3.68)	<.00001
Neurogenic	0.09 (0.05–0.13)	0.04 (0.02–0.05)	0.002	0.06 (0.10–0.01)	2.21 (1.07–4.59)	0.03317
Hormonal	0.17 (0.11–0.22)	0.08 (0.06–0.10)	<0.001	0.09 (0.15–0.03)	2.29 (1.36–3.87)	0.00194
Hypogonadism	0.05 (0.02–0.08)	0.00 (0.00–0.01)	<0.001	0.05 (0.02–0.08)	9.92 (2.31–42.65)	0.00206
Pharmacogenic	4.16 (3.91–4.41)	3.08 (2.95–3.20)	<0.001	1.09 (1.37–0.80)	1.43 (1.31–1.55)	<.00001
Psychogenic	0.75 (0.64–0.86)	0.28 (0.24–0.32)	<0.001	0.47 (0.59–0.35)	2.36 (1.83–3.03)	<.00001

<sup>a</sup>Difference between detection rate of the target and the control population

<sup>b</sup>Adjusted for pre-existing cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes, smoking and obesity) as well as time of inclusion into the study cohort

<sup>c</sup>Not included as a variable in the multivariate analysis

**Table 4.** Mean age of men with newly detected diagnosis three months post-index prescription (day 0 to day 91)

Category	Target population (n=24,708)			Control population (n=74,124)			p-value
	n	Mean age	SD	n	Mean age	SD	
Vasculogenic	1005	56.7	11.7	2140	57.3	11.4	0.1447
Hypertension	298	60.1	9.5	563	60.8	8.5	0.2618
Hypercholesterolaemia	258	59.1	8.8	322	60.3	9.1	0.1226
Diabetes	171	58.4	10.4	229	62.4	9.0	<.0001
Urologic	110	62.1	7.8	163	64.4	8.3	0.0199
Neurogenic	23	55.0	13.1	28	63.4	9.4	0.0112
Hormonal	41	58.2	12.2	58	63.7	11.3	0.0221
Hypogonadism	13	60.5	12.1	3	68.0	7.8	0.3315
Pharmacogenic	1028	57.7	11.8	2280	58.4	11.2	0.1132
Psychogenic	185	51.2	12.0	208	55.4	13.2	0.0013

SD, standard deviation; p-values were based on two-sided two-sample t-tests

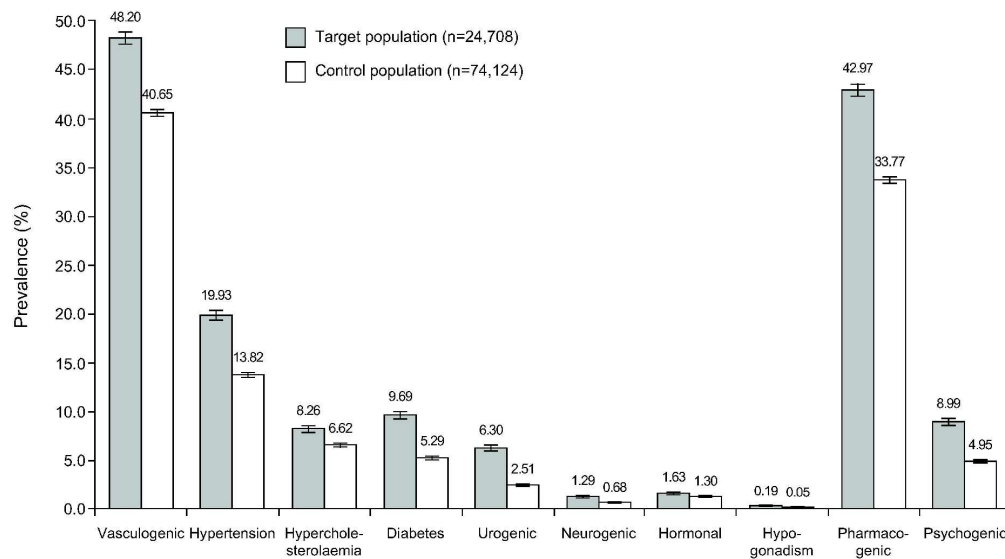


Figure 1. Prevalence (% and 95% CI) of underlying disease in men receiving a PDE5i (target population) and in age-matched controls without a PDE5i prescription (control population). All differences between target and control populations were significant ( $p < 0.001$ ).  
156x85mm (600 x 600 DPI)

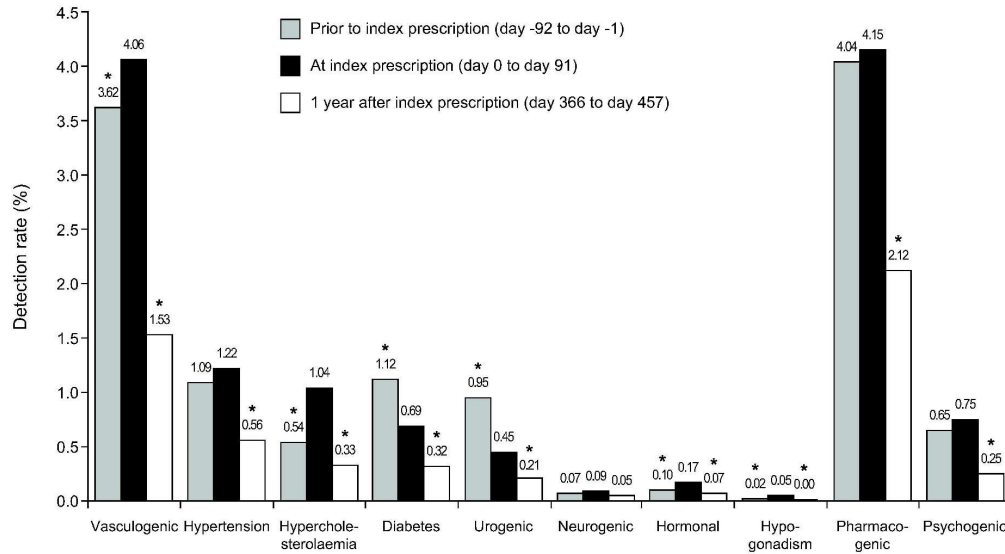


Figure 2. Comparison of detection rates (%) during the 3 months prior to index prescription (day - 92 to day -1), the three months post-index prescription (day 0 to day 91) and a 3-month period one year after the index prescription (day 366 to day 457). Data for the subgroup target population (n=24,479) with continuous recording over the full time period are presented.

\*p<0.05 compared to the detection rate at index prescription  
155x85mm (600 x 600 DPI)



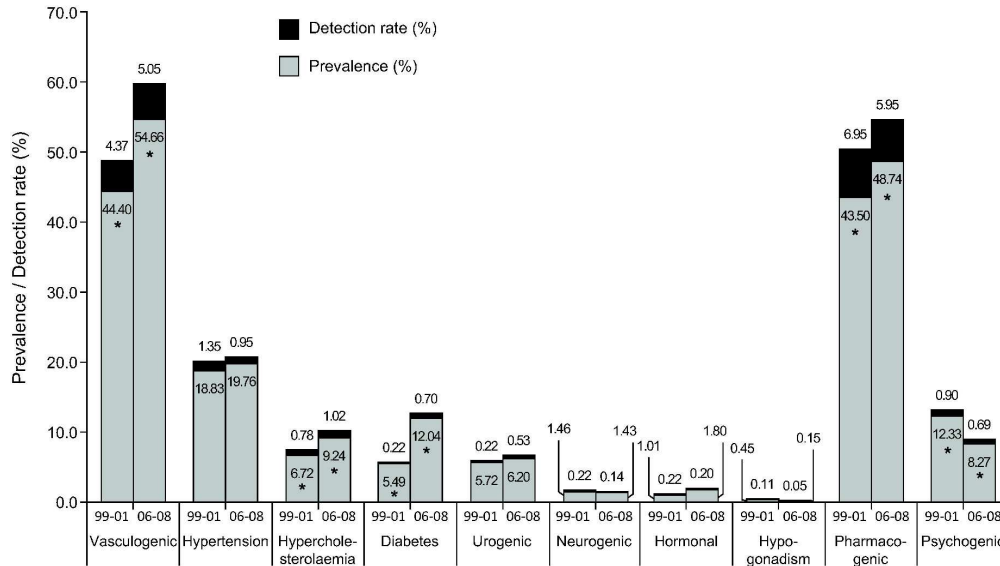


Figure 3. Comparison of prevalence (%) and detection rate (%) of underlying conditions in patients prescribed a PDE5i during the early study period (1999 to 2001; n=892) and the end of the study period (mid 2006 to mid 2008; n=9,862).

\*p<0.05; no significant differences were seen in the detection rates.  
155x87mm (600 x 600 DPI)