GPRD research protocol: matched cohort study of CVD risk associated with exposure to pharmacological smoking cessation interventions

Full title: retrospective, matched cohort study to evaluate cardiovascular disease risk following exposure to pharmacological smoking cessation interventions in a representative UK primary care population

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1. LAY SUMMARY

Preliminary study data have indicated a possible increased cardiovascular disease (CVD) risk in patients exposed to nicotine replacement therapy (NRT) compared with controls (i.e. non-NRT exposed patients) of a magnitude that could not reasonably be accounted for by differences in the cardiovascular (CV) risk profile of the two patient groups. Further in-depth studies in this area are warranted.

This retrospective, matched cohort study will compare the CVD event risk in a group of smokers undertaking unaided smoking cessation attempts with the event rate in a group of smokers attempting smoking cessation assisted by pharmacological interventions, any of NRT, bupropion or varenicline in a representative UK primary care population. There will be a baseline and outcome period designed to assess CVD risk. The baseline period will be a minimum of one year before an index date (IPD) – date of first recorded smoking cessation intervention, either pharmacological or non-pharmacological – for confounder definition. Of primary interest will be the CV event rate over a 4-week outcome period (secondary outcomes periods of of 12, 26 and 56 weeks will also be investigated). Also of interest will be all-cause mortality and survival analysis (i.e. time to first CV event).

2. FINAL PROTOCOL

Objective

This matched cohort study will compare the cardiovascular disease (CVD) event rate in smokers undertaking unaided smoking cessation attempts (the non-exposed group) with the event rate in smokers attempting smoking cessation assisted by pharmacological interventions – by nicotine replacement therapy (NRT) (as any, or a combination, of: nasal spray, transdermal patches, inhaler or gum and tablets) or other pharmacological smoking cessation aids (e.g. bupropion [Zyban®] and varenicline [Champix®]) – in a representative UK primary care population.

Background

Tobacco dependence is a chronic, relapsing condition that the medical community has only recently begun to accept as a disease rather than a vice. The World Health Organization (WHO) officially recognised tobacco dependence as a condition in its own right in 1992, in its International Classification of Diseases (ICD-10).[1]

Smoking prevalence varies greatly between different countries and regions and also considerably between different age groups, those of differing socioeconomic status and between men and women. Across Europe, the economic burden associated with smoking (as a result of lost productivity, premature death and healthcare expenditure) in 2000 was estimated to be between EUR 97.7–130.3 billion.[2] In 2000 alone, tobacco use was responsible for 655,000 deaths among the European Union's 25 Member States. The main causes of death included: cancers (285,000); CVD (183,000); respiratory disease (113,000) and various other conditions (74,000).[3]

Yet in recent years, there has been an awakening of Public consciousness and fuller recognition within the medical community of the irrefutable health implications of tobacco dependence and the benefits afforded by smoking cessation. Improved education and the introduction of

legislation and national smoking bans have undoubtedly played a role in this heightened awareness.

With increasing social and political movement towards provision of smoke-free environments, there is an ever-greater need to provide effective support for those smokers attempting to quit. With smoking cessation becoming an increasingly important component of national and international tobacco control policies and programs, treatment of tobacco dependence will become a key part of primary care.[2]

There are three main types of pharmacological interventions currently available for smoking cessation, each of which has demonstrated efficacy when used in conjunction with behavioural support: NRT, bupropion, and varenicline.[4,5] Others medications, especially nortryptiline and clonidine, are considered to be effective adjunct therapy in smoking cessation, but they remain second-line options at this time.[6]

NRT has been available since the 1980s and bupropion since 2000. Either approach to cessation doubles the chance of achieving abstinence when compared with unsupported quit attempts.[7] After being granted its European licence in 2006, varenicline joined the pharmacological smoking cessation armamentarium. It is the first drug developed specifically for the treatment of tobacco dependence that contains no nicotine, and it triples smokers' chances of quitting compared with unsupported quit attempts.[8]

As the fore-runner, NRT is the longest-standing of the existing pharmacological smoking cessation interventions currently available. It aims to alleviate nicotine withdrawal symptoms by substituting the nicotine attained through tobacco smoking via alternative means (e.g. nasal sprays, inhalers, gum and tablets, transdermal patches). The various NRT products available have differing durations of action and allow patients to tailor their nicotine intake according to their particular needs.[9–12] For example, patches can be used to substitute for background nicotine and gums or tablets can be used to help satisfy urges.

NRT is normally prescribed as monotherapy initially, with subsequent combination therapy (combining various NRT products) if monotherapy proves unsuccessful.

Bupropion was originally licensed as an atypical anti-depressant, but has been proven to be an effective non-nicotine medication for use in smoking cessation.[13–15] It has been shown to be effective in patients who have no depressive symptoms and so its effect on nicotine dependence appears to be quite separate from its antidepressant effect. It inhibits the reuptake of both dopamine and norepinephrine in the central nervous system,[13] and its dopaminergic activity on the pleasure and reward pathways could explain its success in reducing nicotine craving and the symptoms of withdrawal. In addition, it may function as a nicotine acetylcholine receptor antagonist for smoking cessation.[16]

Varenicline has a dual mode of action. It is a partial agonist, which allows it to mimic the effects of nicotine while, simultaneously, acting as an antagonist by preventing nicotine from binding to the receptors in the brain. The approach aims to both suppress nicotine withdrawal symptoms ("agonistic activity") and also limit the standard of reward attained from cigarette smoking ("antagonistic activity").[17]

While all three main smoking cessation pharmacotherapies are licensed for use in the UK, each has a number of known, associated side effects. There are currently no formal criteria available

to assess which pharmacotherapy will prove most effective in a given patient. As a result treatment decisions and choice of first-line therapy are made at the discretion of the clinician, taking into account contraindications and the patient's smoking history and therapy preference.

Rationale for study

In response to anecdotal reports of a possible signal for increased CVD risk in smokers exposed to NRT, an exploratory study was carried out to evaluate the presence of any such risk in these patients.

Preliminary analysis of the data concluded that (when adjusted for history of CVD, age and sex) there was a relative risk of 1.44 (95% CI: 1.17–1.79) for CVD in patients exposed to NRT compared with non-NRT exposed patients; the difference in risk was statistically significant. While the study findings indicate a possible elevated CVD risk associated with NRT exposure, the study authors – of whom Professor Dr David Price (the Chief Investigator of the proposed GPRD follow-up study) – were cautious about drawing any absolute conclusions given the simplistic study design. They argued that the use of only a limited number of covariables and the possibility of confounding if NRT were more readily prescribed to patients who already had high CVD risk should not be overlooked. The study team also noted that the magnitude of risk did not increase with greater length of exposure to NRT.

Further analysis of the preliminary study data considered the possible confounding from known CVD risk factors, such as body mass index (BMI), hyperlipidaemia, systolic blood pressure, hypertension and diabetes. However, the prevalence of diabetes and hyperlipidaemia were similar across the NRT-exposed and non-NRT exposed patients groups and, while the prevalence of hypertension was slightly higher in the non-NRT exposed group, there was practically no difference in BMI and systolic blood pressure. These findings led the study authors to conclude that there were no differences in the cardiovascular risk profile of the two patient groups of sufficient magnitude that could reasonably account for the elevated CVD risk in NRT-exposed compared with non-NRT exposed patients.

Professor Price and the co-investigators of the exploratory study concluded that these exploratory data suggest the need for a more detailed, matched cohort study to investigate further any difference in CVD risk in patients exposed to NRT and other smoking cessation pharmacotherapies compared with that in patients undertaking quit attempts unaided by pharmacotherapies.

Study design

This is a retrospective, matched cohort study consisting of a baseline and outcome period designed to assess CVD risk. The baseline period is a minimum of one year before the index prescription date (IPD) – the date of first recorded smoking intervention, either pharmacological or non-pharmacological – for confounder definition. The primary outcome period is 4 weeks following the IPD for exposed and non-exposed patients (see definitions below), with subsequent, secondary endpoints identified at 12, 26 and 52 weeks post the IPD.

Exposed patients: smokers with no past history of CVD and no recorded smoking cessation attempts using pharmacological aids in the prior year, whose first recorded smoking cessation

intervention was a cessation attempt assisted by one of the following pharmacological smoking cessation interventions at the IPD:

(i) NRT as any, or a combination, of:
- transdermal patches
- nasal spray
- gum and tablets
- inhaler

(ii) Other pharmacological smoking cessation interventions (e.g. bupropion, varenicline).

Non-exposed patients: smokers with no past history of CVD and no recorded smoking cessation attempts using pharmacological aids in the prior year, whose first recorded smoking cessation intervention involved receipt of smoking cessation advice that resulted in a quit attempt unaided by pharmacological therapies at the IPD and during the outcome period (s).

During the 4-week primary outcome period after the IPD, the following will be compared: CV (cardiovascular) events (i.e. incidence or diagnosis of cerebrovascular disease [CerebroVD], incidence or diagnosis of congestive heart disease [CHD]); CV-related mortality (i.e. death resulting from CerebroVD or CHD), CV-related hospitalisations and referrals; all-cause mortality. Initiation of prescribing of cardiovascular-related therapies, which may be indicative of new cardiovascular disease, will also be identified. These will also be evaluated at 12, 26 and 52 weeks post the IPD as secondary measures.

Study period

The study period will run from January 2000 (when bupropion first became available on the UK national health service [NHS]; NRT followed in 2001, and varenicline in 2007) to the end of June 2009, or later if more current data are available. Patients included in the analysis will have been registered for at least one year prior to the IPD, during which they did not undertake any smoking cessation attempts assisted by pharmacotherapy. Outcomes will be evaluated at the end of a 4-week primary follow-up period, and at the subsequent secondary time intervals of 12 weeks, 26 weeks and 52 weeks after the IPD. A 52-year follow-up period may detect any seasonal variations in prevalence of CV events (which may be higher in winter compared with summer months in many temperate climates).[17]

Study population

Inclusion criteria

The analysis will include an exposure group comprising smokers with no past history of CVD and no recorded smoking cessation attempts using pharmacological aids in the prior year, whose first recorded smoking cessation intervention was a cessation attempt assisted by either NRT (using any of, or a combination of products) or another pharmacological smoking cessation intervention (e.g. bupropion, varenicline) at the index date.

Patients must also meet the following inclusion criteria:
- Aged: 18–75 years.

- Have at least one year of up-to-standard (UTS) baseline data as defined by GPRD (prior to the IPD) and at least 4 weeks' of UTS outcome data (following the IPD) or UTS data up to the time of death if death occurred within the outcome period.

The primary period of analysis will be 4 weeks following the IPD looking at CV events in smokers receiving pharmacological smoking cessation interventions.

Exclusion criteria

Patients will be excluded from the analysis if they:

- Have had exposure to any NRT or other pharmacological smoking cessation interventions in the baseline period (year prior to the IPD), and/or
- Switched between types of smoking cessation interventions (i.e. NRT to other pharmacological smoking cessation interventions or vice versa) during the outcome period(s). Switching between different NRT products, or use of multiple NRT products, will be permissible and analysis may involve a comparison of outcomes relative to nicotine exposure over the various outcome periods.

Patients with any of CVD, CHD, Cerebrovascular disease, Angina, Hypertensive prior to IPD will be identified, but not excluded

Selection of comparison group

Inclusion criteria

The analysis will include a non-exposed group comprising smokers with no past history of CVD and no recorded smoking cessation attempts using pharmacological aids in the prior year, whose first recorded smoking cessation intervention involved receipt of smoking cessation advice that resulted in a quit attempt unaided by pharmacological therapies at the IPD and during the outcome periods.

Patients must also meet the following inclusion criteria:

- Aged: 18–75 years.
- Current smoker throughout the prior year (any quantity of cigarettes).
- Received smoking cessation advice at IPD
- Have at least one year of UTS baseline data as defined by GPRD (prior to the IPD) and at least 4 weeks' of UTS outcome data (following the IPD), or UTS data up to the time of death if death occurred within the follow-up period(s).

The primary period of analysis will be 4 weeks following IPD looking at CV events in smokers attempting pharmacologically-unaided smoking cessation attempts.

Exclusion criteria

Patients will be excluded from the analysis if they have had:

- exposure to any of NRT, bupropion, varenicline or other smoking cessation interventions in the baseline period (year prior to the IPD) or outcome period (year following the IPD).

Patients with any of CVD, CHD, Cerebrovascular disease, Angina, Hypertensive prior to IPD will be identified, but not excluded.

Exposures, outcomes and covariates

Exposures

The following exposures are being compared:

Exposed patients: smokers with no past history of CVD and no recorded smoking cessation attempts using pharmacological aids in the prior year, whose first recorded smoking cessation intervention was a cessation attempt assisted by one of the following pharmacological smoking cessation interventions at the IPD:

(i) NRT as:
- transdermal patches
- nasal spray
- gum and tablets
- inhaler

(ii) Other pharmacological smoking cessation interventions (e.g. bupropion, varenicline).

Non-exposed patients: smokers with no past history of CVD and no recorded smoking cessation attempts using pharmacological aids in the years immediately prior to the IPD whose first recorded smoking cessation intervention involved smoking cessation advice that resulted in a quit attempt unaided by pharmacological therapies at the IPD and during the outcome periods.

The non-exposed group has been defined to reflect, as closely as possible, the patients in the exposed group, with the main exception of note being the decision by their physician to provide smoking cessation advice / education only, rather than a pharmacological intervention, at the index date.

<table>
<tr><th>Baseline period</th><th></th><th colspan="8">Follow-up period</th></tr>
<tr><td rowspan="2">Smokers (no history of CVD ever; no history of pharmacological-assisted smoking cessation attempts)</td><td rowspan="2">IPD</td><td rowspan="2">Exposure group*</td><td>NRT (trans-dermal)</td><td>AND / OR</td><td>NRT (inhaler)</td><td>AND / OR</td><td>NRT (nasal spray)</td><td>AND / OR</td><td>NRT (gum & tablets)</td></tr>
<tr><td colspan="7">Pharmacological smoking cessation agent (e.g. bupropion, varenicline)</td></tr>
<tr><td></td><td>Non-exposed group</td><td colspan="7">Smoking cessation advice, but no smoking pharmacological smoking intervention</td></tr>
</table>

*≥1 prescriptions for smoking cessation pharmacotherapy

Outcomes

Primary outcomes

- CV event during 4-week outcome period:
  - CHD diagnosis and No of days from IPD
  - CHD-related death and No Of days from IPD
  - CerebroVD diagnosis and No Of Days from IPD

- CerebroVD death and No of Days from IPD
- Recorded GP consultations or hospital attendances for CHD or CebebroVD, including admission, A&E attendance, out-of-hours or Out-Patient Department (OPD) attendance.

Reporting categories

Results reported for all patients and split by:

- Nicotine exposure during outcome period(s) e.g. varying exposure as a result of using multiple NRT products
- Outcome periods: 4 weeks; 12 weeks; 26 weeks, and 56 weeks Data analyst to only run 52 week outcome period. Statisticians to split into relevant outcome periods as stated(DP-16/05/2011)
- Age group: 18–30; 31–40; 41–50; 51–60, and 61–75 years
- Comorbid disease: diabetes, hypertension
- BMI group: underweight; normal; overweight; obese (see Section 4.4).

Covariates

Prior research in CVD has identified a range of potential confounders that may affect study outcomes. These include a range of demographic and co-morbid factors. Initial analysis will identify the key baseline confounders and outcome analyses will take these findings into account and will utilise appropriate statistical methods (e.g. using logistic regression methods to account for confounding, matching techniques to control for baseline differences) to minimise potential confounding. Index dates from 2000 onwards will be accepted.

Potential confounders examined at (or closest to) the relevant index prescription date:

- Age of patient
- Gender of patient
- Height of patient
- Weight of patient
- Body Mass Index (BMI)

Potential confounders examined regardless of when they occurred relative to the index prescription date:

- Other confounding diagnoses, including:
  - Diabetes
  - Hypertension
  - Angina
  - Dyslipidaemia
  - Rhinitis
  - Smoking history
  - Chronic obstructive pulmonary disease (COPD)
  - Cardiac disease
- Other important unrelated co-morbidities will be expressed using the Charlson Comorbidity Index (CCI).

Potential confounders examined in the year before the index date:

- Number of general practice consultations
- Number of hospital outpatient attendances

- Number of non-specific hospitalisation

Code lists

Code lists using OXMIS, read and drug codes have been, and will continue to be, developed by the researchers, who include part-time academic GPs. These have been developed and refined over the last 3 years in their own research and in collaboration with other academic partners in a large number of primary care database studies. Those making up the CCI have been developed using ICD-9 matching algorithms produced by CLUE.

Statistical analysis

The study will have 80% power to detect an odds ratio of 1.28 at the one-sided 5% significance level assuming the CVD event rate is 0.7% in the NRT group and the sample sizes are 20,000 in the exposed group and 40,000 in the unexposed group.

A detailed statistical analysis plan will be written once the Study Steering Committee has reviewed the baseline data and the optimum approach to sensitivity analyses and adjustment, or matching will be determined. If baseline factors in the the exposed and non-exposed groups are deemed similar, then multiple logistic regression and Cox survival analysis will constitute the primary analysis after adjustment for potential baseline confounders found to be signifcantly different between the two cohorts at $p<0.10$ level. However, if large baseline clinical/statistical differences are found, then the two cohorts will be matched (on as many factors as possible without substantial loss of sensitivity due to missing values). Any factors that we are unable to match on will be included in the multivariate models as conventional adjustments. With matched data, the primary analysis will be conditional logistic regression. A number of pre-specified sub-group analyses will also be performed, although these will not be hypothesis testing (since we are likely to be under powered to detect statistically significant differences across subgroups).

Sensitivity analyses may also be performed to maximise relevant data capture and to interrogate further the data available, e.g. to evaluate any potential impact of nicotine exposure during the outcome periods as a result of use of multiple NRT products, and the potential effect of failed cessation attempts (i.e. restarting smoking) on CV risk during the longer (i.e. 26- and 52-week) secondary outcome periods. Index dates from 2000 onwards will be accepted.

Limitation of the study design, data sources and analytical methods

As with all database studies, a number of limitations exist for which it was not possible to adjust, such as potential confounding factors (e.g. unrecorded over-the counter NRT purchases), with the problem of internal validity

The methods of adjustment used addressed all factors that it is possible to account for. Given the inherent limitations of database studies, however, the study results need to be viewed in conjunction with those of other study designs, in particular RCTs.

Dissemination and communication of study results

In line with ethics around dissemination of findings of potential scientific or public health significance, the study will be registered with clinicaltrials.gov and the initial results will aim to be presented in poster format at appropriate cardiovascular conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in cardiology or cardiovascular medicine. There are no restrictions in terms of when results will be submitted for publication. Submission for publications will aim to be as soon as the analyses are completed and the results are verified.

Patient involvement

Ben Rooke, a patient representative on the Norfolk and Suffolk Comprehensive Local Research Network (CLRN) Board, was consulted and involved in the protocol drafting.

Ethical review

An External Steering Committee will be set up comprising clinical experts in smoking cessation. Data will be reviewed by the Steering Committee following baseline extraction and following outcome analysis.

In terms of overall ethical approval, the study team are aware that the GPRD Group has obtained ethical approval from a Multi-centre Research Ethics Committee (MREC) for all purely observational research using GPRD data. The proposed study meets the ISAC definition of purely observational research – "studies which do not include patient involvement". If ISAC raise any ethical issues during their scientific review of the study protocol and recommend study-specific MREC approval will be sought as required.

Researchers

1. Professor David Price, General Practice Airways Group Professor of Primary Care Respiratory Medicine[a,b]
2. Dr Mike Thomas, Asthma UK Fellow[a]
3. Julie von Ziegenweidt, Data Manager[b]
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Study timings and milestones

Project timings

A summary of the anticipated timelines for the various steps and overall completion of the study are detailed below. The third column indicates the dates at which each of the detailed steps would be completed by if there project were to commence as of 1 February 2010.

Study step	Tasks involved	Predicted duration	Timings for completion of step (1/02/10 start date)
Data extraction	Produce code list; set up databases; extract datasets; revise rulesets and extraction process	~7 weeks	12/03/10
Baseline data review	Internal review by study group; external review by Steering Committee	~1 week	19/03/10 Baseline data could be presented at an appropriate research meeting held at this time
Statistical analysis[*]	Analysis of extracted data in line with Statistical Analysis Plan	~6 weeks	3/05/10
Outcome data review	Internal review by study group; external review by Steering Committee	~1 week	11/05/10 Outcome data could be presented at an appropriate research meeting held at this time
Data revisions	Revision of data following outcome review meeting	~1 week	18/05/10
Report writing	Generation of statistical report for study from protocol, SAP, etc followed by internal and external review	~4 weeks	16/06/10
Manuscript writing[**]	Drafting a study manuscript for submission to a peer review journal – internal and external review prior to submission	~4 weeks	28/07/10

*Where baseline data review indicates the need for a matched analysis to be performed, the statistical analysis is anticipated to take ~8 weeks due to the additional data extraction time required to optimise the matching approach

**Actual publication of data will be subject to the peer review and manuscript copy editing and typesetting lead times of the journal selected for publication.

3. DATA SOURCE

The dataset used for this analysis is the General Practice Research Database (GPRD). It consists of all patients with smoking history, prescribed pharmacological smoking cessation

interventions and evidence of CVD events, diagnoses and treatment at any time during the period 1 January 2000 to 30 June 2007.

Products of interest will include those listed in the following chapters of *British National Formulary* (*BNF*):
Pharmacological smoking cessation interventions

- Chapter 4.10

CV-related pharmacological therapies

- Chapter 2.

4. ANALYSIS RULES

4.1. Inclusion/Exclusion criteria

Patients must be current smokers (any quantity of cigarettes) during the prior year, and at, the date the first recorded smoking cessation intervention (either advice or pharmacological therapy) is initiated (i.e. at

Patients will be excluded from the analysis if they have had exposure to any of NRT or other smoking cessation pharmacotherapies in the year prior to IPD, or have had a CVD read code at any time prior to the IPD. The CVD code list includes: history of CHD or CerebroVD or incidence of CHD or CerebroVD Have had a CVD read code or CV prescriptions at any time prior to the IPD. The CVD code list includes: history of CHD or CerebroVD or incidence of CHD or CerebroVD or angina so as to eliminate (as far as is possible) patients with markers of early CVD.

Patient cohorts

IPDC NRT cohort defined as patients in whom NRT (in any preparation) was initiated at the IPD as the first recorded smoking cessation intervention.

IPDC OTH cohort defined as patients in whom other (non-NRT) smoking cessation pharmacotherapies were initiated at the IPD (e.g. bupropion, varenicline) as the first recorded smoking cessation intervention.

IPDC CONT cohort (control patients) defined as patients whose first recorded smoking cessation intervention involved smoking cessation advice leading to a quit attempt unassisted by pharmacological smoking cessation aids, at the IPD.

4.2. Time period

The primary period of analysis will be 4-weeks following the IPD and will evaluate the primary endpoints of CVD event incidence.

Secondary time intervals will be defined as 12 weeks, 26 weeks and 52 weeks after the IPD, at which point the endpoint of CVD event incidence will also be evaluated. A 52-year follow-up period may be able to detect seasonal variation in prevalence of CV event incidence (which may be higher in winter compared with summer months in many temperate climates).[17]

Patients must have at least one year of UTS baseline data as defined by GPRD (prior to the IPD) and at least 4 weeks of UTS outcome data (following the IPD), or UTS data up to the time of death if death occurred before the end of the 4-week outcome period, for the primary analysis. UTS outcome data up to 12, 26 and 52 weeks (or up to the time of death if death occurred within the defined outcome period) will be required (as appropriate) for outcome evaluation at of each of the secondary time periods defined.

Patients must be current smokers (any quantity of cigarettes) during the prior year and at time the smoking cessation intervention is initiated (at IPD).

4.3. Determining outcomes

Composite proxy CV event defined as:
Any of the following recorded in the primary (4-week) and secondary (12-, 26- and 52-week) outcome periods:

(i) CHD diagnosis and No days from IPD
(ii) CHD-related death and No days from IPD
(iii) CerebroVD diagnosis and No days from IPd
(iv) CerebroVD death and No days from IPD
(v) Recorded GP consultations or hospital attendance for CHD or CebebroVD, including admission, A&E attendance, out-of-hours attendance, or OPD attendance.

4.4. Height and weight

Last recorded measurements prior to IPD.

Height

Adults: 1.4 metres < height < 2.2 metres

Weight

Adult: 40kg < weight < 200kg

Standard BMI classifications[18]

Health classification	BMI
Underweight	18.5 or lower
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obese	30 or higher

4.5. Dyslipidaemia

Last recorded measurements prior to IPD.
Definitions and classifications of dyslipidaemia[19]

- Total cholesterol (TC) >5.0 mmol/l, OR
- Low-density lipoprotein cholesterol (LDL-C) >3.0 mmol/l, OR
- High-density lipoprotein cholesterol (HDL-C):
  - Men <1.0 mmol/l,
  - Women <1.2 mmol/l, OR
- Triglycerides (TG) >1.7 mmol/l

4.6. Blood pressure and hypertension

Last recorded measurements prior to IPD.

Definitions and classifications of blood pressure levels (mmHg)[18]

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	8084
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

5. APPENDICES

APPENDIX A. Terminology

A&E – Accident and Emergency
CerebroVD – Cerebrovascular disease
CHD – Congestive heart disease
CV – Cardiovascular
CVD – Cardiovascular disease
GPRD – General Practice Research Database
HDL-C – High-density lipoprotein cholesterol
IMD – Index of Multiple Deprivation
IPD – Index prescription date
LDL-C – Low-density lipoprotein cholesterol
NHS – National Health Service
NRT – Nicotine replacement therapy
OPD – Out-Patient Department
SES – Socioeconomic status
SOA – Super output areas
TC – Total cholesterol
TG – Triglycerides
UK – United Kingdom
WHO – World Health Organization

APPENDIX B. Socioeconomic calculation

SES has been assigned to practices using the Index of Multiple Deprivation (IMD) as a proxy measure. IMD was captured for the whole of the UK in 2000, divided into England, Wales, Scotland and Northern Ireland. The IMD for Scotland and England were updated in 2004. An update for Wales is expected in summer 2005.

The IMD is derived by weighted contributions for a number of different categories. These categories are weighted differently for England, Scotland, Wales and Northern Ireland.

They involve a selection of the following for each nation:

- Income
- Employment
- Health Deprivation & Disability
- Education Skills & Training
- Barriers to Housing & Services
- Crime
- Living Environment
- Health
- Housing
- Geographic Access & Telecommunications
- Geographical Access to services

The relative contributions and dates of the IMD generation for the different countries are summarised below:

	England IMD 2004	Northern Ireland IMD 2000	Scotland IMD 2004	Wales IMD 2000
	Percentage each component represents in the IMD			
Income	22.50	25.00	28.57	25.00
Employment	22.50	25.00	28.57	25.00
Health Deprivation & Disability	13.50	15.00		15.00
Education Skills & Training	13.50	15.00	14.29	15.00
Barriers to Housing & Services	9.33	10.00		
Crime	9.33	5.00		
Living Environment	9.33	5.00		
Health			14.29	
Housing			4.76	10.00
Geographic Access & Telecommunications			9.52	
Geographical Access to services				10.00
Total	100	100	100	100

GPRD have linked the SES to small areas using the practice postcode where possible. 2004 data are more detailed than that of 2000, defining the IMD to smaller areas. These areas are called Super Output Areas (SOA) in England and Data zones in Scotland. IMD from 2000 is linked to electoral wards (Northern Ireland) and electoral divisions (Wales).

SES scores and quintiles

A high score indicates high deprivation. This is represented also by a high rank. e.g. rank=4, score=70. The least deprived areas will have a low score and a low rank (e.g. 0). Due to the scores being generated separately for each country, the quintile categories are all set relative to the range of scores in a country specific manner.

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