ARTICLE

Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study

**Evangelos Kontopantelis · David A. Springate ·
David Reeves · Darren M. Ashcroft · Martin Rutter ·
Iain Buchan · Tim Doran**

Abstract

Aims/hypothesis We aimed to describe the shape of observed relationships between risk factor levels and clinically important outcomes in type 2 diabetes after adjusting for multiple confounders.

Methods We used retrospective longitudinal data on 246,544 adults with type 2 diabetes from 600 practices in the Clinical Practice Research Datalink, 2006–2012. Proportional hazards regression models quantified the risks of mortality and microvascular or macrovascular events associated with four modifiable biological variables (HbA$_{1c}$, systolic BP, diastolic BP and total cholesterol), while controlling for important patient and practice covariates.

Results U-shaped relationships were observed between all-cause mortality and levels of the four biometric risk factors. Lowest risks were associated with HbA$_{1c}$ 7.25–7.75% (56–61 mmol/mol), total cholesterol 3.5–4.5 mmol/l, systolic BP 135–145 mmHg and diastolic BP 82.5–87.5 mmHg. Coronary and stroke mortality related to the four risk factors in a positive, curvilinear way, with the exception of systolic BP, which related to deaths in a U-shape. Macrovascular events showed a positive and curvilinear relationship with HbA$_{1c}$ but a U-shaped relationship with total cholesterol and systolic BP. Microvascular events related to the four risk factors in a curvilinear way: positive for HbA$_{1c}$ and systolic BP but negative for cholesterol and diastolic BP.

Conclusions/interpretation We identified several relationships that support a call for major changes to clinical practice. Most importantly, our results support trial data indicating that normalisation of glucose and BP can lead to poorer outcomes. This makes a strong case for target ranges for these risk factors rather than target levels.

E. Kontopantelis · D. A. Springate · D. Reeves
NIHR School for Primary Care Research, Centre for Primary Care, Institute of Population Health, University of Manchester, Manchester, UK

E. Kontopantelis (✉) · I. Buchan
Centre for Health Informatics, Institute of Population Health, University of Manchester, Vaughan House, Portsmouth Street, Manchester M13 9GB, UK
e-mail: e.kontopantelis@manchester.ac.uk

D. A. Springate · D. Reeves
Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, UK

D. M. Ashcroft
Centre for Pharmacoepidemiology and Drug Safety Research, Manchester Pharmacy School, University of Manchester, Manchester, UK

M. Rutter
Endocrinology and Diabetes Research Group, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK

M. Rutter
Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

T. Doran
Department of Health Sciences, University of York, York, UK

Abbreviations

CPRD	Clinical Practice Research Datalink
MNAR	Missing not at random
NHS	National Health Service
NIHR	National Institute for Health Research
ONS	Office of National Statistics
QOF	Quality and Outcomes Framework
SPCR	School for Primary Care Research

Introduction

Diabetes affects nearly 300 million globally and contributes to
over 10% of adult deaths, mainly through related cardiovascular
and renal disease [1]. In the UK, direct treatment costs
are estimated at £9.8 billion ($16.3 billion)—over 10% of the
total National Health Service (NHS) budget—with further
indirect costs of £4 billion ($6.7 billion) [2]. Type 2 diabetes
accounts for 90–95% of all cases, is linked with the obesity
'epidemic' and is considered to be largely preventable [3].

The key requirements for management of type 2 diabetes
are now well established and centre on lifestyle management
(diet, weight control, smoking cessation, physical activity),
primary and secondary prevention (glucose, BP and lipid
control, monitoring and treatment of retinopathy, neuropathy
and nephropathy) and, when necessary, referral to specialist
services [4–7]. Consensus has not been reached, however, on
how best to deliver these requirements or on optimal levels of
control for biometric variables. For example, guidelines gen-
erally advise control of HbA$_{1c}$ levels to below 7.0%
(53 mmol/mol) in North America and 7.5% (58.5 mmol/
mol) in the UK but evidence has emerged that intensive
control of blood glucose does not increase longevity, is asso-
ciated with higher risk of cardiovascular death (particularly in
younger patients [8]) and increases the risk of severe
hypoglycaemia [9, 10]. Similarly, BP control below 130/
80 mmHg was recently found not to reduce all-cause mortality
in newly diagnosed diabetes patients [11]. Other studies dem-
onstrated a U-shaped relationship between HbA$_{1c}$ levels and
all-cause mortality, which is possibly attributable to residual
confounding through unmeasured variables [12]. For exam-
ple, patients in the later stages of cancer often have low plasma
glucose levels, where the elevated risks of adverse outcomes
are due to the cancer not the hypoglycaemia. Non-linear
relationships have also been observed for the association
between patient outcomes and BP (with the lowest risk of
coronary events associated with systolic pressures of 120–
130 mmHg [13, 14]) and lipid levels [15, 16]. Causality,

however, is again difficult to establish due to confounders
such as the use of statins.

Given such uncertainties, a greater understanding of the
effect of risk factors on outcomes for diabetic patients in real-
world settings is required. In this study we used a large
longitudinal database of individual patient records to quantify
the relationship between biological variables (HbA$_{1c}$, BP and
cholesterol levels) and key outcomes for type 2 diabetes,
including complications and mortality, while controlling for
time-varying patient and practice covariates (e.g. comorbidi-
ties and area deprivation). As far as we know this is the first
investigation that attempts to control analyses for various
comorbidities and thus limit residual confounding, while
using novel methodologies to account for missing values
and simultaneously examine the relationship between all key
biological variables (biometrics) and outcomes.

Methods

Data source We used the Clinical Practice Research Datalink
(CPRD), a large primary care database that holds complete
electronic patient records (including diagnoses, prescriptions
and referrals) from participating family practices across the
UK. A hierarchical clinical coding system (Read) is used to
record the data. In July 2012, data were available for 644
practices and 13,772,992 patients. Full details of the database
have been provided elsewhere [17].

Diabetes cohort We extracted data from 1 April 2006 to 31
March 2012 and, for ease of reporting and analysing, aggre-
gated information into six financial years. Within each year,
practice inclusion eligibility was determined by a CPRD
assessment algorithm, which informs on practices considered
to be of research standard; therefore, our cohort of practices
varied over time. For each research standard practice and year,
we defined as eligible patients those who were registered with
the practice for the full year and were aged 18 years or over in
that year. From these patients, using relevant Read codes for
type 2 diabetes (e.g. C10F.00: Type 2 diabetes mellitus) and
excluding those treated with insulin within 2 years of diagno-
sis, we identified 246,544 patients over the study period.
Diagnoses were not constrained to the study period and a
relevant code prior to the study as well as during the study
period would flag a patient from the respective year onwards.
Data on sex, age and removal from the database due to deaths
were available and complete for all patients. We extracted data
on diabetes-related macrovascular (myocardial infarction,
stroke, peripheral vascular disease or amputation) and micro-
vascular (retinopathy, neuropathy, nephropathy [chronic kid-
ney disease stages 4–5] or foot ulcer) complications as well as
comorbidities (asthma, coronary heart disease, chronic kidney
disease [excluded from microvascular analysis], chronic

obstructive pulmonary disease, depression, dementia, severe mental illness, heart failure, hypertension, stroke [excluded from macrovascular analysis], cancer, epilepsy, osteoarthritis, osteoporosis and hypothyroidism). Although we aimed to include all conditions associated with diabetes, the choice was partially determined by the domains incentivised under the Quality and Outcomes Framework (QOF), for which accuracy of diagnosis is considered high [18]. Information was also extracted on smoking (never smoked, current, ex-smoker and missing data), BMI, HbA_{1c} levels (%), cholesterol levels (mmol/l) and systolic/diastolic BP (mmHg). Biometric measurement data were cleaned and we calculated patient means for each year when more than one relevant record was available. Using product lists we determined prescription prevalence (at least one) for relevant medications: ACE inhibitors, acarbose, α-blockers, anticoagulants, antiplatelet agents, β-blockers, calcium-channel blockers, thiazide diuretics, loop diuretics, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists, statins and other lipid-lowering drugs, meglitinides, metformin, sulfonylureas and thiazolidinediones. For approximately 60% of the practices, records were linked to Office of National Statistics (ONS) mortality data and we had access to death dates for all their patients. For these, using ICD-10 codes (www.who.int/classifications/icd/en/) we were able to estimate deaths linked to specific causes (underlying or in the top three): diabetes (E10–E16), ischaemic heart disease (I21–I22), stroke (I60–I64) or stroke excluding bleeds (excluding I63). All code lists used are available for download from www.clinicalcodes.org [19].

Statistical modelling We used Cox (proportional hazards) regressions to investigate mortality and first new diabetes-related complication events in relation to the risk factors. For many patients, data for risk factors were less complete in the year of their death. For this reason, and to avoid reverse causality, when considering mortality we excluded data on these variables in the year of death. For first new macrovascular or microvascular diabetes complication (cases with any previous record of complication were excluded), missing data in the year of complication diagnosis was not an issue and they were modelled without a time lag. Separate analyses were performed for each complication type and mortality: all-cause (via CPRD and ONS record linkage); diabetes; coronary; stroke (ischaemic, haemorrhagic). Each model included HbA_{1c}, cholesterol and systolic and diastolic BP as potentially explanatory variables. We included systolic and diastolic BP measurements as separate predictors in the models, rather than use an aggregate pulse pressure measure, since they demonstrated different relationship patterns with the outcomes and the correlation between them was only moderate (Pearson's $r=0.49$, after imputation), while UK, US and other international guidelines for controlling BP, target

systolic and diastolic pressures rather than pulse pressure. Additional covariates to control for possible confounding were age, sex, each comorbidity, BMI, microvascular and macrovascular complications (not if outcome), smoking and practice characteristics (diabetes prevalence, list size, region, area deprivation). We used Schoenfeld residuals to test the proportional hazards assumption and included time-varying covariates when needed to stabilise the models.

Due to the nature of the modelled variables (e.g. each comorbidity was identified by the presence of a relevant code), data was complete except for risk factor levels (BMI, HbA_{1c}, BP and total cholesterol levels) and smoking status. For BMI, we used an interpolation algorithm to clean and impute missing values between observations over time. For all analyses, risk factor levels were categorised and for the main analyses missing data were coded as an additional category (Fig. 1 and electronic supplementary material [ESM] 1 Figs 1–7). However, we also employed 'twofold', a multiple-imputation algorithm for longitudinal data, which uses data within and across time to impute missing biometric measurements [20]. Through this approach we generated five complete datasets with which we conducted sensitivity analyses using multiple-imputation techniques. Additional sensitivity analyses for all-cause mortality were run in a subsample of patients aged 65 years or younger (to see if the patterns were similar in a younger population) and with a 2 and 3 year time lag on mortality (to verify that patterns were unaffected by biometric changes immediately prior to death, possibly due to frailty). Further sensitivity analyses for all-cause mortality examined whether patterns differed according to sex or to polypharmacy level. We defined three levels of polypharmacy using the 33rd and 66th centile of the count of medication groups a patient was prescribed on average within a year (medication groups are shown in Table 1). All analyses were performed using Stata v13 (StataCorp, College Station, TX, USA) and commands stcox and mi estimate. In ESM 1 and ESM 2 we provide more methodological details, discuss the role of BMI and provide the sensitivity analyses results.

Results

Patient characteristics The characteristics of the cohort are summarised in Table 1. Overall, recorded type 2 diabetes prevalence rose from 2.8% (148,570 patients) in 2006/2007 to 3.3% (166,718 patients) in 2011/2012 with the increase being greater in more deprived areas. In 2011/2012 prevalence ranged from 2.9% in the most affluent fifth of areas to 4.0% in the most deprived. Prevalence rates were highest in Wales, the East Midlands and the North-West of England. Between 2006/2007 and 2011/2012, the mean age of patients increased slightly from 66.1 to 66.4 years; the percentage of female

Fig. 1 Hazard ratios (CIs) for HbA$_{1c}$ level (**a**), cholesterol level (**b**), systolic BP (SBP) (**c**) and diastolic BP (DBP) (**d**) on all-cause CPRD mortality in the following year (main analysis). The standard dataset with time-varying covariates was used. The second category shown in all graphs represents the reference category. The missing category for diastolic BP has been omitted as it is perfectly collinear with the missing category for systolic BP. To convert values for HbA$_{1c}$ in DCCT % into mmol/mol, subtract 2.15 and multiply by 10.929
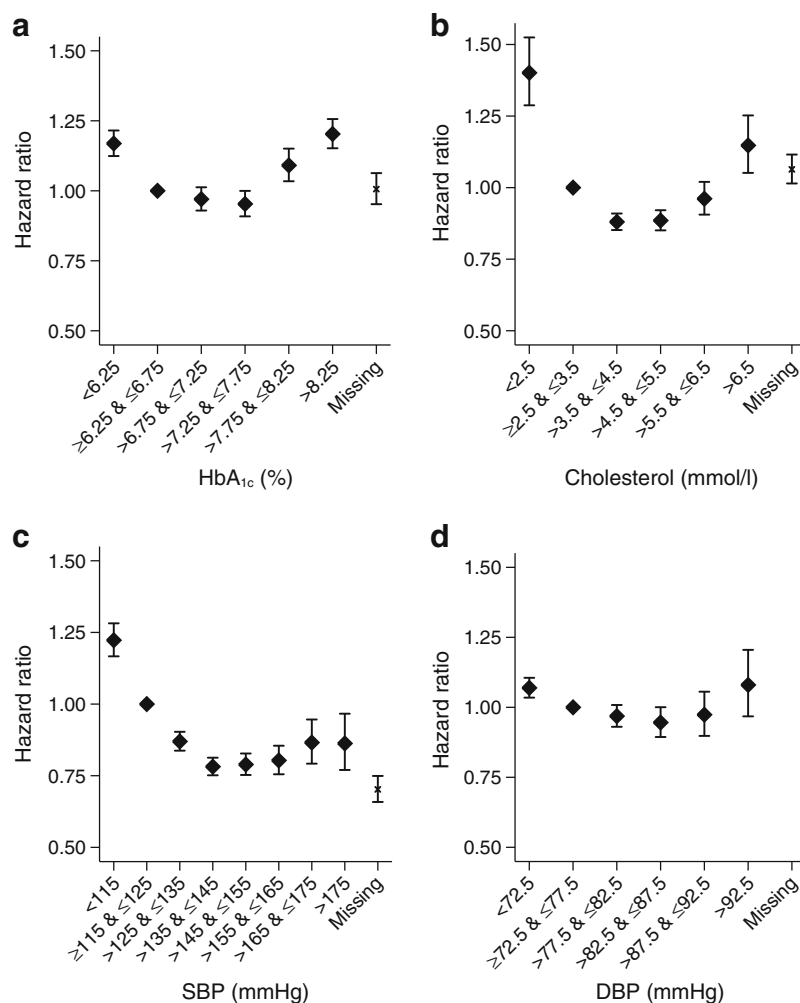
patients remained constant at 44% to 45%; the mean diabetes duration increased from 6.8 to 7.8 years and the mean age at diagnosis dropped from 59.3 to 58.5 years.

The recorded prevalence of the first occurrence of a new microvascular complications rose from 21.9% in 2006/2007 to 33.0% in 2011/2012, while first new macrovascular complications dropped from 18.3% to 16.9% over the same period. Annual mortality rates varied between 3.3% and 3.7%: approximately a quarter of deaths were linked to diabetes; 10% to ischaemic heart disease and 10% to stroke. Over the study period, mean HbA$_{1c}$ levels remained stable at between 7.3% (56.3 mmol/mol) and 7.4% (57.4 mmol/mol), mean systolic BP fell from 138 to 136 mmHg, mean diastolic BP fell slightly from 77 to 76 mmHg and mean cholesterol levels fell from 4.4 to 4.3 mmol/l. BMI averaged around 31 in all years, while 15% of patients were recorded as current smokers and 65% as ex-smokers.

Prevalence of key medications and comorbidities are reported in Table 1. Statins, ACE inhibitors and metformin were the most widely prescribed drugs, while prescriptions for dipeptidyl peptidase-4 inhibitors and thiazolidinediones

increased over time. Hypertension was by far the most commonly recorded comorbidity (>60%), followed by osteoarthritis (≈27%), depression (≈25%), chronic kidney disease (≈20%) and coronary heart disease (≈19%). More information on numbers of comorbidities is provided in ESM 1 Table A1.

Main analyses Adjusted hazard ratios for mortality and complication events vs the differing levels of HbA$_{1c}$, total cholesterol and BP are shown in Table 2.

We observed U-shaped relationships between all-cause CPRD mortality and the mean levels of vascular risk factors (HbA$_{1c}$, total cholesterol and BP), with both low and high levels associated with more deaths (Fig. 1). The HbA$_{1c}$ level associated with the minimum mortality risk was 7.5±0.25% (56–61 mmol/mol). Compared with patients with HbA$_{1c}$ levels of 6.5±0.25% (45–50 mmol/mol), hazard ratios for mortality were greater for patients with mean HbA$_{1c}$ levels <6.25% (45 mmol/mol) (1.17; 95% CI 1.12, 1.22), 8.0± 0.25% (61–67 mmol/mol) (1.09; 95% CI 1.03, 1.15) and >8.25% (67 mmol/mol) (1.20; 95% CI 1.15, 1.26). The total

Table 1 Characteristics for the study population, 2006–2012

Characteristic	2006/2007	2007/2008	2008/2009	2009/2010	2010/2011	2011/2012
Diabetes (type 2) prevalence (%)						
Overall	2.8	2.9	3.0	3.1	3.2	3.3
By practice area deprivation quintile						
1 (most affluent)	2.4	2.5	2.6	2.7	2.8	2.9
2	2.6	2.7	2.8	2.9	3.0	3.1
3	2.8	2.9	3.0	3.1	3.2	3.3
4	2.9	3.0	3.1	3.2	3.3	3.3
5 (most deprived)	3.3	3.4	3.6	3.7	3.8	4.0
By country						
England	2.8	2.9	3.0	3.1	3.3	3.3
Northern Ireland	2.5	2.7	2.8	3.0	3.1	3.3
Scotland	2.8	2.9	3.0	3.2	3.3	3.4
Wales	3.4	3.5	3.6	3.8	3.9	4.1
By area in England						
North-East	2.7	2.8	2.9	3.0	3.1	3.1
North-West	3.1	3.3	3.4	3.5	3.8	3.9
Yorkshire-Humber	2.6	2.8	3.3	3.4	3.5	3.5
East Midlands	3.2	3.3	3.4	3.7	4.0	4.0
West Midlands	2.9	3.0	3.1	3.2	3.3	3.4
East of England	2.6	2.7	2.8	2.9	3.1	3.2
South-West	2.6	2.6	2.7	2.8	2.9	3.0
South-Central	2.3	2.4	2.5	2.5	2.6	2.6
London	2.8	2.9	2.9	3.0	3.1	3.2
South-East	2.7	2.8	2.9	3.0	3.1	3.2
Database counts						
No. of practices	569	566	565	556	534	499
No. of registered patients	5,321,351	5,370,801	5,449,547	5,432,224	5,301,520	5,069,748
No. of type 2 diabetes patients[a]	148,570	155,359	163,843	168,951	170,797	166,718
Cohort demographics (type 2 diabetes patients only)						
Mean age, years (SD)	66.1 (12.7)	66.1 (12.7)	66.2 (12.7)	66.3 (12.8)	66.3 (12.8)	66.4 (12.8)
% Female sex	45.0	44.9	44.6	44.3	44.1	44.0
Mean age at diagnosis, years (SD)	59.3 (13.2)	59.1 (13.2)	59.0 (13.2)	58.9 (13.1)	58.8 (13.1)	58.5 (13.0)
Mean duration of condition, years (SD)	6.8 (6.8)	7.0 (6.8)	7.2 (6.8)	7.4 (6.8)	7.6 (6.8)	7.8 (6.8)
Macrovascular complications prevalence						
% All	18.3	18.0	17.8	17.5	17.2	16.9
% Peripheral vascular disease	5.0	4.9	4.8	4.7	4.5	4.4
% Myocardial infarction	8.2	8.1	8.1	8.0	7.9	7.8
% Stroke	4.4	4.4	4.3	4.2	4.2	4.1
% Amputation	0.6	0.6	0.6	0.6	0.6	0.6
Microvascular complications prevalence						
% All	21.9	23.9	26.2	28.6	30.9	33.0
% Retinopathy	14.7	16.5	18.7	21.0	23.2	25.2
% Neuropathy	4.4	4.5	4.6	4.7	4.8	5.0
% Chronic kidney disease (stages 4–5)	1.1	1.3	1.3	1.3	1.3	1.3
% Nephropathy (excluding chronic kidney disease stages 4–5)	0.6	0.6	0.5	0.5	0.5	0.5
% Foot ulcer	1.0	1.0	1.0	1.0	1.0	1.0
% Neuropathic foot ulcer	0.1	0.1	0.1	0.1	0.1	0.1
Macrovascular complications incidence[b]						
% Yes (when none before)	1.2	1.1	1.1	1.0	1.0	1.0
Denominator	123,263	129,116	136,543	141,171	143,210	140,176

Table 1 (continued)

Characteristic	2006/2007	2007/2008	2008/2009	2009/2010	2010/2011	2011/2012
Microvascular complications incidence[c]						
% Yes (when none before)	4.8	4.5	4.8	4.8	4.8	4.6
Denominator	123,144	125,141	128,779	128,710	126,304	119,358
Death in next year						
% Yes	3.7	3.7	3.4	3.4	3.3	
Denominator	143,929	150,880	159,026	163,941	165,579	
ONS death in next year						
% Yes	3.9	3.7	3.6	3.6	2.6	
Denominator	86,842	92,745	97,390	100,221	99,094	
ONS death in next year (cause: diabetes)						
% Yes	0.9	0.9	0.8	0.9	0.6	
Denominator	86,842	92,745	97,390	100,221	99,094	
ONS death in next year (cause: ischaemic heart disease)						
% Yes	0.4	0.3	0.3	0.3	0.2	
Denominator	86,842	92,745	97,390	100,221	99,094	
ONS death in next year (cause: stroke)						
% Yes	0.4	0.3	0.3	0.3	0.2	
Denominator	86,842	92,745	97,390	100,221	99,094	
ONS death in next year (cause: stroke no bleeds)						
% Yes	0.3	0.3	0.3	0.3	0.2	
Denominator	86,842	92,745	97,390	100,221	99,094	
Smoking[d]						
% Current smoker	15.1	14.6	14.6	14.5	14.5	14.5
% Ex-smoker	65.1	65.4	65.2	65.2	64.8	64.8
% Missing[e]	0.6	0.5	0.3	0.2	0.1	0.0
BMI[f]						
Average; mean (SD)	30.6 (6.3)	30.8 (6.4)	30.9 (6.4)	31.0 (6.4)	31.0 (6.4)	31.0 (6.4)
% Missing[e]	5.8	5.9	5.8	6.2	7.1	12.9
HbA$_{1c}$, (%)						
Average; mean (SD)	7.4 (1.4)	7.4 (1.4)	7.4 (1.4)	7.3 (1.4)	7.4 (1.4)	7.4 (1.4)
Last; mean (SD)	7.3 (1.5)	7.3 (1.5)	7.3 (1.4)	7.3 (1.4)	7.3 (1.5)	7.4 (1.5)
Count; mean (SD)	1.8 (1.1)	1.7 (1.1)	1.8 (1.1)	2.9 (2.1)	3.4 (2.2)	2.8 (1.9)
% Missing[e]	9.3	9.6	9.1	8.9	8.2	8.2
HbA$_{1c}$ (mmol/mol)						
Average; mean (SD)	57.4 (15.3)	57.4 (15.3)	57.4 (15.3)	56.3 (15.3)	57.4 (15.3)	57.4 (15.3)
Last; mean (SD)	56.3 (16.4)	56.3 (16.4)	56.3 (15.3)	56.3 (15.3)	56.3 (16.4)	57.4 (16.4)
Systolic BP (mmHg)						
Average; mean (SD)	137.7 (14.6)	137.2 (14.4)	136.7 (14.3)	136.4 (14.2)	135.9 (14.1)	135.6 (13.9)
Last; mean (SD)	136.0 (16.2)	135.7 (16.0)	135.3 (15.8)	135.0 (15.6)	134.6 (15.4)	134.0 (15.1)
Count; mean (SD)	3.4 (2.8)	3.2 (2.7)	3.2 (2.8)	3.1 (2.6)	3.0 (2.5)	3.0 (2.5)
% Missing[e]	4.9	5.3	5.2	5.5	5.3	5.1
Diastolic BP (mmHg)						
Average; mean (SD)	77.0 (8.7)	76.8 (8.7)	76.6 (8.7)	76.5 (8.7)	76.2 (8.7)	76.2 (8.7)
Last; mean (SD)	76.1 (9.9)	76.0 (9.8)	75.9 (9.7)	75.8 (9.8)	75.5 (9.7)	75.4 (9.6)
Count; mean (SD)	3.4 (2.8)	3.2 (2.7)	3.2 (2.8)	3.1 (2.6)	3.0 (2.5)	3.0 (2.5)
% Missing[e]	4.9	5.3	5.2	5.5	5.3	5.1
Cholesterol level (mmol/l)						
Average; mean (SD)	4.4 (1.0)	4.3 (1.0)	4.3 (1.0)	4.3 (1.0)	4.3 (1.0)	4.3 (1.0)
Last; mean (SD)	4.3 (1.0)	4.3 (1.0)	4.3 (1.0)	4.3 (1.0)	4.3 (1.0)	4.3 (1.1)
Count; mean (SD)	1.5 (1.0)	1.5 (1.0)	1.5 (1.0)	1.5 (1.0)	1.4 (1.0)	1.4 (1.0)
% Missing[e]	10.2	10.7	10.6	11.1	11.1	11.0

Table 1 (continued)

Characteristic	2006/2007	2007/2008	2008/2009	2009/2010	2010/2011	2011/2012
Diabetes medication (%)[g]						
Acarbose	0.7	0.6	0.5	0.4	0.3	0.3
Dipeptidyl peptidase-4 inhibitor	0.0	0.3	1.3	3.6	6.4	8.5
Glucagon-like peptide-1 agonist	0.0	0.2	0.7	1.7	2.6	3.2
Meglitinide	0.7	0.7	0.7	0.6	0.5	0.4
Metformin	55.6	57.3	59.6	62.0	64.9	65.8
Sulfonylurea	32.7	32.3	32.2	32.3	32.0	31.9
Thiazolidinedione	3.9	5.5	7.1	7.5	8.9	8.1
Cardiovascular medication (%)[g]						
ACE inhibitor	64.5	65.5	65.9	65.7	65.4	64.8
α-Blocker	10.5	10.2	9.9	9.8	9.5	9.2
Anticoagulant	5.5	5.6	5.8	6.0	6.1	6.3
Antiplatelet	53.1	54.3	54.4	51.1	45.7	41.9
β-Blocker	27.6	25.9	25.8	25.7	25.6	25.7
Calcium−channel blocker	33.6	34.1	34.2	34.4	34.2	34.2
Thiazide diuretic	26.2	24.9	23.9	22.9	22.2	21.4
Other lipid-lowering drug	5.6	6.5	7.0	7.2	7.1	6.6
Loop diuretics	17.2	16.8	16.5	16.0	15.7	15.2
Statins	74.9	75.9	77.1	77.5	76.7	76.3
Comorbidities: count						
Mean (SD) no. of conditions[h]	2.0 (1.5)	2.1 (1.5)	2.1 (1.5)	2.1 (1.5)	2.1 (1.5)	2.1 (1.5)
Comorbidities: prevalence (%)						
Asthma	9.3	9.4	9.6	9.6	9.5	9.4
Coronary heart disease	21.1	20.6	20.0	19.3	18.7	18.1
Chronic kidney disease	17.8	20.9	21.6	21.7	21.4	21.1
Chronic obstructive pulmonary disease	4.4	4.7	4.9	5.0	5.1	5.3
Depression	22.2	23.1	23.7	24.2	24.7	25.4
Dementia	1.5	1.6	1.6	1.8	2.0	2.1
Severe mental illness	1.9	2.0	2.1	2.2	2.3	2.4
Heart failure	5.8	5.4	5.1	4.9	4.7	4.6
Hypertension	62.7	63.2	63.2	63.1	62.7	62.2
Stroke	9.2	9.1	8.9	8.8	8.8	8.6
Cancer	7.2	7.5	7.8	8.0	8.3	8.7
Epilepsy	1.0	1.0	1.0	1.0	1.0	1.0
Osteoarthritis	25.0	25.7	26.4	26.7	27.1	27.2
Osteoporosis	2.7	2.9	3.0	3.1	3.2	3.3
Hypothyroidism	9.1	9.5	9.6	9.7	9.8	9.9

[a] Aged 18 years or over

[b] Peripheral vascular disease, myocardial infarction, stroke or amputation

[c] Retinopathy, neuropathy, nephropathy, chronic kidney disease stages 4–5 or foot ulcer

[d] Information from previous years is used to define cases. Patients are classed as active smokers if associated with at least one relevant code at any time until the end of the respective year and no cessation or ex-smoker code has interjected. Missing cases relate to patients for which no relevant codes are available (non-smoker, active smoker, ex-smoker or cessation) until the end of the respective year

[e] Percentage of patients with no record

[f] After applying BMI interpolation-imputation algorithm, BMI data were extracted from 1 April 2000 to 31 March 2012, to maximise the efficiency of the algorithm. The higher rates for missing values for the last years are explained by the nature of the algorithm: a value for a 'middle' year was more likely to be imputed since extrapolations were not allowed

[g] Percentage of patients with at least one prescription within the year

[h] From the listed conditions, excluding type 2 diabetes

Count, number of measurements within the respective time period; Last, last available measurement within the respective time period

Table 2 Hazard ratios (95% Cis) from Cox proportionate hazards survival analysis for all CPRD deaths, all ONS coronary heart disease-related deaths, all ONS cerebrovascular-related deaths and new diabetes complications (main analysis)[a]

Characteristic	All-cause mortality[b]	Coronary heart disease-related mortality[c]	Cerebrovascular-related mortality[d]	Macrovascular complication(s)[e]	Microvascular complication(s)[f]
Age	1.066 (1.063, 1.070)[g]	1.085 (1.070, 1.099)[g]	1.098 (1.083, 1.113)[g]	1.029 (1.026, 1.033)[g]	1.006 (1.004, 1.008)[g]
Male sex	1.247 (1.213, 1.282)	1.504 (1.328, 1.704)	0.971 (0.857, 1.101)	1.427 (1.362, 1.495)	1.109 (1.061, 1.158)[g]
Complications					
Macrovascular	1.259 (1.173, 1.350)[g]	2.141 (1.877, 2.443)	1.600 (1.405, 1.822)		
Microvascular	1.157 (1.126, 1.189)	1.218 (1.082, 1.371)	1.098 (0.973, 1.238)	1.426 (1.362, 1.492)	
Smoking					
Never smoked	Reference				
Ex-smoker	1.250 (1.149, 1.359)[g]	1.217 (1.029, 1.440)	1.047 (0.904, 1.213)	1.331 (1.152, 1.538)[g]	0.970 (0.945, 0.994)
Current smoker	1.844 (1.645, 2.067)[g]	1.874 (1.512, 2.321)	1.232 (0.984, 1.542)	2.024 (1.701, 2.408)[g]	0.945 (0.912, 0.978)
Missing	0.503 (0.389, 0.650)	0.258 (0.036, 1.848)	1.221 (0.538, 2.772)	3.436 (1.714, 6.887)[g]	1.058 (0.847, 1.323)
Practice characteristics					
Diabetes prevalence	0.942 (0.910, 0.974)[g]	0.983 (0.916, 1.054)	0.959 (0.896, 1.027)	0.941 (0.917, 0.965)	1.136 (1.107, 1.165)[g]
List size (1,000s)	0.997 (0.995, 1.000)	0.996 (0.985, 1.007)	1.000 (0.989, 1.011)	0.995 (0.991, 1.000)	1.025 (1.022, 1.028)[g]
Region[i]					
North-West	Reference				
North-East	0.881 (0.801, 0.970)	0.624 (0.419, 0.929)	0.736 (0.492, 1.101)	1.448 (1.260, 1.664)	1.746 (1.636, 1.864)
Yorkshire-Humber	0.879 (0.814, 0.948)	0.924 (0.716, 1.194)	0.964 (0.729, 1.274)	0.837 (0.731, 0.957)	1.028 (0.963, 1.097)
East Midlands	0.811 (0.748, 0.879)	0.820 (0.602, 1.117)	1.032 (0.751, 1.418)	0.907 (0.796, 1.033)	1.317 (1.244, 1.395)
West Midlands	0.929 (0.880, 0.980)	0.788 (0.646, 0.962)	0.913 (0.743, 1.122)	0.770 (0.701, 0.846)	1.253 (1.201, 1.307)
East of England	0.879 (0.831, 0.930)	0.781 (0.636, 0.960)	0.926 (0.752, 1.141)	0.840 (0.764, 0.925)	0.673 (0.611, 0.742)[g]
South-West	0.907 (0.859, 0.958)	0.771 (0.633, 0.939)	0.953 (0.779, 1.166)	0.801 (0.729, 0.881)	1.437 (1.378, 1.499)
South-Central	0.941 (0.892, 0.992)	0.842 (0.681, 1.042)	0.955 (0.767, 1.189)	0.829 (0.758, 0.907)	0.980 (0.904, 1.061)[g]
London	0.822 (0.779, 0.867)	0.661 (0.534, 0.818)	0.959 (0.779, 1.181)	0.823 (0.755, 0.897)	1.112 (1.068, 1.158)
South-East Coast	0.793 (0.704, 0.895)[g]	0.348 (0.200, 0.606)[g]	0.829 (0.666, 1.033)	0.822 (0.750, 0.901)	0.988 (0.945, 1.033)
Northern Ireland	0.950 (0.881, 1.024)			0.988 (0.874, 1.116)	0.438 (0.364, 0.525)[g]
Scotland	1.062 (1.008, 1.118)			0.977 (0.897, 1.064)	1.242 (1.156, 1.334)[g]
Wales	1.006 (0.958, 1.056)			0.874 (0.803, 0.952)	1.007 (0.934, 1.086)[g]
Deprivation quintile					
1 (most affluent)	Reference				
2	1.108 (1.063, 1.156)	0.939 (0.777, 1.135)	1.139 (0.942, 1.377)	1.052 (0.980, 1.130)	0.954 (0.924, 0.986)
3	1.070 (1.026, 1.115)	0.991 (0.821, 1.195)	1.161 (0.957, 1.409)	1.079 (1.006, 1.157)	0.888 (0.860, 0.918)
4	1.093 (1.049, 1.139)	0.922 (0.764, 1.112)	1.081 (0.889, 1.315)	1.056 (0.985, 1.132)	0.894 (0.856, 0.933)[g]
5	1.124 (1.076, 1.174)	1.020 (0.838, 1.241)	1.225 (0.999, 1.501)	0.999 (0.927, 1.076)	0.891 (0.839, 0.947)[g]
Comorbidities					
Asthma	1.066 (1.020, 1.114)	0.936 (0.764, 1.148)	0.966 (0.780, 1.195)	1.025 (0.954, 1.102)	0.996 (0.963, 1.030)
Coronary heart disease	1.042 (1.012, 1.072)[g]	1.367 (1.208, 1.546)	0.846 (0.743, 0.963)	2.959 (2.737, 3.199)[g]	1.022 (0.997, 1.048)
Chronic kidney disease	1.179 (1.099, 1.265)	1.577 (1.399, 1.776)	1.151 (1.025, 1.294)	1.151 (1.094, 1.211)	
Chronic obstructive pulmonary disease	1.821 (1.649, 2.012)[g]	1.113 (0.908, 1.365)	0.994 (0.792, 1.246)	1.516 (1.264, 1.819)[g]	1.049 (1.003, 1.097)
Depression	1.046 (1.015, 1.078)	0.979 (0.858, 1.117)	1.032 (0.905, 1.177)	1.125 (1.070, 1.182)	1.067 (1.015, 1.122)[g]
Dementia	1.702 (1.493, 1.940)[g]	0.959 (0.724, 1.270)	1.699 (1.395, 2.069)	1.188 (1.043, 1.354)	0.851 (0.782, 0.926)
Serious mental illness	1.469 (1.303, 1.656)[g]	1.146 (0.802, 1.637)	1.039 (0.748, 1.445)	1.173 (1.024, 1.344)	0.938 (0.874, 1.007)
Heart failure	1.733 (1.673, 1.795)	2.070 (1.795, 2.387)	1.651 (1.416, 1.926)	1.710 (1.588, 1.842)	1.361 (1.306, 1.418)
Hypertension	1.033 (1.005, 1.062)	1.131 (0.996, 1.283)	1.108 (0.974, 1.260)	1.137 (1.083, 1.193)	1.037 (1.015, 1.059)
Stroke	1.097 (1.060, 1.136)	0.852 (0.731, 0.991)	2.713 (2.387, 3.083)		1.150 (1.066, 1.241)[g]
Cancer	3.026 (2.801, 3.270)[g]	0.965 (0.814, 1.145)	1.200 (1.025, 1.405)	1.081 (1.009, 1.159)	1.040 (1.005, 1.077)
Epilepsy	1.487 (1.331, 1.662)[g]	0.783 (0.450, 1.362)	2.097 (1.502, 2.926)	1.504 (1.245, 1.817)	0.995 (0.902, 1.098)
Osteoarthritis	0.943 (0.918, 0.969)	0.836 (0.742, 0.942)	1.012 (0.903, 1.134)	1.065 (1.017, 1.116)	1.064 (1.040, 1.088)

Table 2 (continued)

Characteristic	All-cause mortality[b]	Coronary heart disease-related mortality[c]	Cerebrovascular-related mortality[d]	Macrovascular complication(s)[e]	Microvascular complication(s)[f]
Osteoporosis	1.106 (1.049, 1.167)	1.290 (1.020, 1.631)	1.105 (0.890, 1.371)	1.139 (1.026, 1.265)	1.051 (0.994, 1.111)
Hypothyroidism	0.987 (0.949, 1.026)	0.829 (0.689, 0.997)	0.881 (0.741, 1.048)	1.009 (0.941, 1.082)	1.017 (0.984, 1.051)
BMI					
<18.5	2.083 (1.923, 2.256)	1.745 (1.131, 2.693)	1.658 (1.152, 2.386)	1.234 (0.979, 1.556)	0.784 (0.675, 0.911)
≥18.5 & ≤25	Reference				
>25 & ≤30	0.603 (0.572, 0.635)[g]	0.826 (0.704, 0.968)	0.693 (0.594, 0.808)	0.868 (0.816, 0.923)	0.963 (0.903, 1.027)[g]
>30 & ≤40	0.529 (0.499, 0.561)[g]	0.785 (0.661, 0.933)	0.533 (0.444, 0.639)	0.753 (0.670, 0.847)[g]	0.852 (0.799, 0.909)[g]
>40	0.809 (0.753, 0.870)	1.145 (0.848, 1.547)	0.580 (0.387, 0.869)	0.679 (0.608, 0.757)	0.799 (0.724, 0.881)[g]
Missing BMI	3.140 (3.023, 3.262)	3.545 (2.964, 4.238)	2.617 (2.219, 3.086)	1.293 (1.177, 1.421)	0.706 (0.628, 0.794)[g]
HbA$_{1c}$ (%)					
<6.25 (<45 mmol/mol)	1.169 (1.124, 1.215)	1.023 (0.854, 1.226)	1.169 (0.979, 1.396)	0.975 (0.906, 1.050)	0.976 (0.945, 1.008)
≥6.25 & ≤6.75 (45–50 mmol/mol)	Reference				
>6.75 & ≤7.25 (50–56 mmol/mol)	0.970 (0.929, 1.013)	0.938 (0.773, 1.137)	1.084 (0.892, 1.318)	1.038 (0.966, 1.117)	1.024 (0.992, 1.058)
>7.25 & ≤7.75 (56–61 mmol/mol)	0.953 (0.909, 1.000)	0.970 (0.788, 1.194)	1.205 (0.976, 1.487)	1.086 (1.004, 1.174)	1.065 (1.029, 1.103)
>7.75 & ≤8.25 (61–67 mmol/mol)	1.091 (1.034, 1.151)	1.123 (0.894, 1.411)	1.366 (1.079, 1.730)	1.190 (1.091, 1.298)	1.103 (1.060, 1.148)
>8.25 (>67 mmol/mol)	1.203 (1.152, 1.256)[h]	1.323 (1.102, 1.589)	1.314 (1.072, 1.611)	1.460 (1.360, 1.566)	1.273 (1.233, 1.314)[h]
Missing HbA$_{1c}$	1.006 (0.952, 1.063)	0.957 (0.739, 1.240)	1.249 (0.971, 1.608)[h]	1.280 (1.139, 1.439)	0.772 (0.726, 0.820)
Total cholesterol (mmol/l)					
<2.5	1.401 (1.288,1.525)	1.090 (0.706, 1.682)	1.071 (0.673, 1.705)	1.442 (1.225, 1.697)	1.293 (1.182, 1.414)
≥2.5 & ≤3.5	Reference				
>3.5 & ≤4.5	0.880 (0.852, 0.909)	1.033 (0.890, 1.199)	0.878 (0.757, 1.019)	0.904 (0.855, 0.955)	0.953 (0.928, 0.978)
>4.5 & ≤5.5	0.885 (0.851, 0.921)	1.188 (0.997, 1.414)	0.961 (0.808, 1.142)	0.915 (0.856, 0.977)	0.939 (0.911, 0.968)[h]
>5.5 & ≤6.5	0.961 (0.906, 1.020)	1.612 (1.267, 2.050)	0.920 (0.708, 1.195)	0.882 (0.796, 0.977)	0.926 (0.886, 0.969)
>6.5	1.147 (1.051, 1.252)	2.624 (1.958, 3.518)	1.365 (0.972, 1.917)	1.294 (1.136, 1.474)	0.967 (0.905, 1.034)[h]
Missing total cholesterol	1.064 (1.014, 1.115)	1.143 (0.911, 1.436)	0.854 (0.677, 1.078)	0.880 (0.795, 0.973)	0.945 (0.901, 0.992)
Systolic BP (mmHg)					
<115	1.223 (1.167, 1.282)	1.284 (1.024, 1.611)	1.132 (0.882, 1.453)	1.171 (1.059, 1.294)	1.021 (0.971, 1.074)
≥115 & ≤125	Reference				
>125 & ≤135	0.870 (0.837, 0.903)	0.806 (0.669, 0.970)	1.064 (0.884, 1.279)[h]	0.963 (0.898, 1.032)	1.068 (1.034, 1.103)
>135 & ≤145	0.782 (0.751, 0.813)	0.981 (0.819, 1.174)	0.952 (0.789, 1.148)	0.936 (0.873, 1.004)	1.096 (1.060, 1.132)
>145 & ≤155	0.789 (0.753, 0.828)	0.950 (0.768, 1.175)	1.031 (0.834, 1.276)	1.077 (0.994, 1.167)	1.193 (1.148, 1.239)
>155 & ≤165	0.803 (0.755, 0.855)	1.326 (1.044, 1.685)	0.926 (0.702, 1.220)	1.289 (1.166, 1.425)	1.256 (1.195, 1.320)
>165 & ≤175	0.866 (0.792, 0.946)	1.110 (0.770, 1.600)	1.089 (0.757, 1.568)	1.506 (1.311, 1.729)[h]	1.289 (1.197, 1.388)
>175	0.863 (0.770, 0.966)	1.321 (0.855, 2.042)	1.466 (0.985, 2.184)	1.637 (1.372, 1.952)	1.447 (1.318, 1.589)
Missing systolic BP	0.702 (0.658, 0.749)	0.697 (0.497, 0.977)	0.610 (0.445, 0.837)[h]	0.508 (0.434, 0.595)	0.788 (0.733, 0.847)
Diastolic BP (mmHg)					
<72.5	1.069 (1.035, 1.105)	1.066 (0.921, 1.235)	0.862 (0.746, 0.997)	0.973 (0.919, 1.029)	1.043 (1.015, 1.072)
≥72.5 & ≤77.5	Reference				
>77.5 & ≤82.5	0.969 (0.930, 1.008)	0.895 (0.748, 1.072)	0.889 (0.748, 1.058)	0.907 (0.851, 0.966)	0.942 (0.915, 0.970)
>82.5 & ≤87.5	0.946 (0.894, 1.000)	0.846 (0.663, 1.079)[h]	0.835 (0.658, 1.061)	0.855 (0.786, 0.929)	0.970 (0.936, 1.005)
>87.5 & ≤92.5	0.974 (0.898, 1.056)	0.740 (0.515, 1.065)	1.119 (0.821, 1.526)	0.832 (0.741, 0.934)	0.956 (0.911, 1.002)
≥92.5	1.080 (0.968, 1.205)	1.307 (0.886, 1.928)	1.239 (0.827, 1.858)	0.996 (0.863, 1.150)	0.917 (0.860, 0.978)
Missing diastolic BP	Omitted[j]				
Model information					
No. of patients	195,481	118,291	118,291	183,140	183,610
No. of failures	24,752	1,340	1,323	8,901	39,553

Table 2 (continued)

Characteristic	All-cause mortality[b]	Coronary heart disease-related mortality[c]	Cerebrovascular-related mortality[d]	Macrovascular complication(s)[e]	Microvascular complication(s)[f]
Years at risk (no. of observations)	689,140	418,792	418,792	710,068	641,955
Log pseudolikelihood	−232,137	−11,661	−11,376	−88,612	−408,639

[a] Models include time-varying covariates so that the proportionate hazard assumption can be met; missing data for biometric measurements have been categorised as such enabling us to use all available records

[b] CPRD estimated deaths in the following year, using data from all available practices

[c] ONS deaths in the following year where the underlying cause (or in top three causes) is ischaemic heart disease (ICD-10 codes I21-I22), using data for approximately 60% of the practices for which the data has been linked

[d] ONS deaths in the following year where the underlying cause (or in top three causes) is stroke (ICD-10 codes I60-I64), using data for approximately 60% of the practices for which the data has been linked

[e] New macrovascular complication (peripheral vascular disease, myocardial infarction, stroke or amputation) in the current year, when none previously, using data from all available practices. Stroke was not included as a covariate in this analysis since it overlaps fully with the outcome. Coronary heart disease and heart failure were included since they do not overlap fully with myocardial infarction

[f] New microvascular complication (retinopathy, neuropathy, nephropathy [chronic kidney disease stages 4–5] or foot ulcer) in the current year, when none previously, using data from all available practices. Chronic kidney disease was not included as a covariate in this analysis since there is great overlap with the outcome

[g] Variables for which additional time-varying components have been added and therefore interpretation of the 'main' effects is not straightforward

[h] Displaying better fit when included an additional logarithmic time-varying component, which implies that the associated hazard increases over time at a logarithmic rate

[i] ONS data only available for England

[j] Omitted since missing cases for SBP and DBP overlap completely

cholesterol level associated with the minimum mortality risk was 4.0±0.5 mmol/l. Compared with patients with mean total cholesterol levels in the reference range 3.0±0.5 mmol/l, hazard ratios were greater for patients with mean levels <2.5 mmol/l (1.40; 95% CI 1.29, 1.53) and >6.5 mmol/l (1.15; 95% CI 1.05, 1.25). For BP, less evident U-shaped relationships were observed. The systolic and diastolic BP associated with the lowest mortality risk was 140±5 and 85±2.5 mmHg, respectively. Higher systolic BP was associated with lower risk compared with the reference category (115–125 mmHg), although the risk seemed to increase for very high systolic BP. However, the highest risk was observed for pressures below 115 mmHg (1.22; 95% CI 1.17, 1.28). For diastolic BP, only pressures below 75 mmHg were linked with a statistically significant increase in mortality (1.07; 95% CI 1.03, 1.11), compared with the reference range (72.5–77.5 mmHg).

Results were similar for all-cause ONS mortality and broadly similar for diabetes-related mortality (ESM 1 Figs 5, 6 and Table 2). However, for the latter, hazard ratios for HbA$_{1c}$ levels more resembled a J-shape pattern, with increased risks for high levels, especially above 8.25% (67 mmol/mol) (1.49; 95% CI 1.33, 1.70). The pattern was different for coronary heart disease-related mortality, with statistically significant increased risks observed only for high values of HbA$_{1c}$ and cholesterol (ESM 1 Fig. 1). For HbA$_{1c}$ levels above 8.25% (67 mmol/mol) the hazard ratio was 1.32 (95% CI 1.10, 1.59),

and for cholesterol levels above 5.5 and up to 6.5 mmol/l or above 6.5 mml/l, the hazard ratios were 1.61 (95% CI 1.27, 2.05) and 2.62 (95% CI 1.96, 3.52), respectively. For cerebrovascular (stroke)-related mortality high values of diastolic BP, cholesterol and HbA$_{1c}$ suggested higher risk, but CIs were much wider due to fewer deaths (ESM 1 Fig. 2). Only HbA$_{1c}$ levels above 7.75 and up to 8.25% (61–67 mmol/mol) or above 8.25% (67 mmol/mol) demonstrated a statistically significant increase in risk, with hazard ratios of 1.37 (95% CI 1.08, 1.73) and 1.31 (95% CI 1.07, 1.61), respectively. Patterns of results were similar when we excluded cerebrovascular deaths attributed to haemorrhage (ESM 1 Fig. 7, Table 2).

For both new macrovascular and new microvascular diabetes complications, patterns were almost linear for HbA$_{1c}$, with increased levels associated with higher risk of developing at least one complication (ESM 1 Figs 3, 4). For example, compared with an HbA$_{1c}$ level of 6.25–6.75% (45–50 mmol/mol), hazard ratios for levels above 8.25% (67 mmol/mol) were 1.46 (95% CI 1.36, 1.57) for macrovascular and 1.27 (95% CI 1.23, 1.31) for microvascular complications, respectively. The relationship with systolic BP seemed linear for new microvascular complications, but U-shaped for macrovascular complications. Compared with the reference range (115–125 mmHg), levels below 115 mmHg were associated with higher macrovascular risk (1.17; 95% CI 1.06, 1.29) and levels above 175 mmHg were associated with increased risk for both macrovascular (1.64; 95% CI 1.37, 1.95) and

microvascular complications (1.45; 95% CI 1.32, 1.59). Cholesterol levels above 3.5 and up to 6.5 mmol/l indicated a small but statistically significant risk reduction compared with the reference category (2.5–3.5 mmol/l), for both complication types. However, values above 6.5 mmol/l were associated with increased risk for macrovascular complications (1.29; 95% CI 1.14, 1.47), while values below 2.5 mmol/l were associated with hazard ratios of 1.44 (95% CI 1.23, 1.70) for macrovascular and 1.29 (95% CI 1.18, 1.41) for microvascular complications. The picture was less clear for diastolic BP, with values above 77.5 and up to 92.5 mmHg suggesting a small reduction in macrovascular risk, while a smaller but statistically significant microvascular risk reduction was observed for values above 92.5 mmHg.

Missing values for cholesterol and, especially, BP were found to be significant predictors of outcome in most analyses, while missing HbA_{1c} values were predictors of complications. This implies that the missing completely at random (MCAR) assumption of a complete-case analysis could not be justified in some survival models and sensitivity analyses with multiple-imputation techniques would be informative. In most cases, missing data were associated with better outcomes, compared with the reference category, implying that measurements are more likely to be missing when patients are healthier.

Sensitivity analyses Results with multiple-imputation methods were broadly similar to results without imputation although in some cases the U-shaped relationships were slightly more pronounced and the effects of extreme ranges were marginally higher (ESM 1 Tables 3, 4, ESM 1 Figs 8–15). The only exception was all-cause mortality vs diastolic BP, for which the estimated risk for high BP was markedly high and statistically significant (ESM 1 Figs 8, 13). For example, for diastolic BP above 92.5 mmHg, the hazard ratio was 1.26 (95% CI 1.14, 1.41) and 1.28 (95% CI 1.12, 1.46) in the CPRD and ONS deaths, respectively.

Relationship patterns were generally similar in the 2 and 3 year mortality analyses, except for systolic BP where the U-shape relationship became much more pronounced with an increase in mortality for higher values. For the younger subcohort (aged ≤65 years), U-shaped relationships for HbA_{1c}, total cholesterol and systolic BP appeared more extreme, while the pattern for diastolic BP was similar. Patterns were similar for male and female patients (with the exception of high systolic BP values) and different polypharmacy levels, indicating that the risk for confounding by severity is small (ESM 2).

Discussion

We found that higher levels of three key factors (HbA_{1c}, total cholesterol and BP) were generally associated with higher risks of adverse outcomes for patients with type 2 diabetes, but we also saw several U-shaped relationships—particularly with mortality—even after adjusting for important confounders.

Strengths and limitations of the study Our analysis advances current knowledge in several areas: (1) it assessed risks for mortality and several diabetes-related complications associated with levels of three modifiable risk factors; (2) it used a large longitudinal database of individual patient records; (3) it adjusted for several important comorbidities and time-varying covariates; and (4) it dealt with missing data using sophisticated multiple-imputation techniques. The observed prevalence of diabetes was lower in our study than has been reported elsewhere [21] but we excluded patients with type 1 diabetes and those receiving insulin within 2 years of diagnosis. Without these exclusions, prevalence rates were closer to national estimates.

Although the cohort size gave us the statistical power to investigate cause-specific mortality and to incorporate important covariates, some important limitations exist. First, diabetes and other comorbidities were identified from practice populations using relevant code lists and algorithms and were not verified cases. Although we do not expect false positives to be a serious issue [22], we will not have identified undiagnosed patients or those who rarely visit their general practice. Second, the list of comorbidities used was not exhaustive. Third, measurements of biological variables are subject to error, particularly in the case of BP, which is measured using instruments of variable accuracy and is prone to digit bias in recording [23]. Also, since 2004, UK practices have had financial incentives for controlling BP and there is evidence to show that recordings of systolic BP have been biased downwards for patients with values just above the target levels (target levels for diabetic patients were 145 mmHg from 2004/2005 to 2010/2011 and 140 mmHg from 2011/2012) [24]. Fourth, some risk factor measurements might be missing not at random (MNAR), as our analyses assume, although multiple imputation offers some protection against biased estimates [25, 26]. Fifth, late registration of deaths through the ONS meant that the proportion of deaths captured is lower for later years in the coverage period, which might have led to an underestimation of the risks. However, the CPRD death algorithm provides a more complete picture for later years and the results for these two death outcomes agree closely. Sixth, we ignored the effect of covariates within the year of death, since we would have many missing values for that year and imputing them all would have been problematic. Seventh, we only assessed the development of first complications, and the risks associated with subsequent complications may not follow the same pattern. Eighth, each risk factor could have a different time-varying relationship with each outcome, confounded by unmeasured confounders. Ninth, we used a yearly

time window, which is suboptimal for survival analysis, but our choice was driven by QOF recording practices. A smaller time window would introduce more missing data under MNAR mechanisms. Tenth, CPRD practices use a single computer system and differences have been found across systems used in England [27]. Finally, data are observational and relationships between risk factor levels and clinical outcomes may be affected by unmeasured confounding.

Findings compared with previous studies Recent trials have found that intensive glucose control is associated with increased risk of cardiovascular death in younger patients [8] and observational studies have generally demonstrated U-shaped relationships between levels of HbA_{1c} in diabetic patients and death [28, 29], possibly attributable to residual confounding through unmeasured variables [12]. In our study we adjusted for several important confounders, including comorbidities such as heart failure, chronic obstructive airways disease and chronic kidney disease. We also adjusted for BMI, low values of which are often associated with severe comorbidity, frailty and hypoglycaemia. Nevertheless, we still found U-shaped relationships between HbA_{1c} levels and cerebrovascular and all-cause mortality—HbA_{1c} values below 6.25% (45 mmol/mol) and above 7.75% (61 mmol/mol) were associated with increased risk. The risk of coronary heart disease-related death increased with HbA_{1c} levels in a more linear fashion, as did the risk of complications.

We found similar patterns for total cholesterol, with a minimum risk of complications and death for patients with levels in the 3.5–5.5 mmol/l range. Interpreting these findings is more difficult, as clinical trials of aggressive cholesterol lowering have not demonstrated increased risk of mortality [30, 31] and there is no obvious explanation for low cholesterol causing diabetes-related microvascular complications. Residual confounding is a possible explanation. Patients with very low total cholesterol levels are more likely to be receiving high-dose statin therapy for severe (generalised) vascular disease and in our cohort 86.8% of patients with mean annual cholesterol levels below 2.5 mmol/l were prescribed statins, compared with 54.5% of those whose levels were above 6.5 mmol/l. Severe vascular disease is associated with poorly controlled long-duration diabetes, and this may be the underlying cause of the higher risk for microvascular complications. However, we observed almost identical results after excluding patients who were prescribed statins.

Aggressive BP control in type 2 diabetes has been found not to reduce major cardiovascular events [32], and U-shaped relationships have recently been described between BP and mortality and cardiovascular outcomes [11, 33]. We found that these relationships persisted after adjusting for important confounders. This may be attributable to under-perfusion of vital organs, but we observed a higher risk of mortality for systolic BP in the 125–135 mmHg range, which would not be expected to cause under-perfusion. Residual confounding from unmeasured variables, such as frailty and undiagnosed heart failure, may therefore have contributed to these findings.

Conclusions Our findings from this inclusive population-level investigation confirm and expand on trial evidence from more selected populations [34, 35], concerning the management of HbA_{1c} and BP but not total cholesterol. Further corroboration is necessary, particularly in prospective longitudinal trials but, if validated, the findings have several implications for type 2 diabetes management. Current clinical guidelines aim to control HbA_{1c} to below 7.0% (53 mmol/mol) in North America and 7.5% (58 mmol/mol) in the UK, and to keep BP below 140/80 mmHg [36, 37]. The UK QOF pay-for-performance scheme uses targets of 7.5% (58 mmol/mol), 8% (64 mmol/mol) and 9% (75 mmol/mol) for HbA_{1c}, 140/80 and 150/90 mmHg for BP and 5 mmol/l for total cholesterol. Our results suggest that achieving these targets may not optimise patient outcomes. For example, we found that HbA_{1c} values above 7.75% (61 mmol/mol) were associated with higher risks of adverse outcomes, suggesting that two of the QOF quality targets (HbA_{1c} ≤8% [64 mmol/mol] and ≤9% [75 mmol/mol]) may reward practices for achieving levels that could increase patient risk of complications and death.

Current guidelines only aim to keep HbA_{1c} below a target value. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study indicated that aggressive glucose lowering in type 2 diabetes (to normalise HbA_{1c} below 6% [42 mmol/mol]) leads to increased mortality compared with a conventional HbA_{1c} target of 7–8% (53–64 mmol/mol) [10]. In our data, strong U-shaped relationships between HbA_{1c} and mortality persisted even after adjusting for important confounders, raising concerns about potential harms from aggressive glucose lowering. Our data, combined with trial data, would argue for controlling HbA_{1c} within a given range (e.g. 6.0–7.5% [42–58 mmol/mol]) rather than below an upper limit. Recent EASD and ADA guidelines recommend individualised HbA_{1c} targets based on factors including age, diabetes duration and the presence of vascular disease and comorbidity [38]. Our results suggest that range-based targets may also be more appropriate for other diabetic risk factors, including total cholesterol and BP. Optimal management of these multiple biological variables in patients with type 2 diabetes is complex and there are still many unknowns to be addressed before we can be confident that we are getting it right.

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