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Cardiovascular risk reduction following diagnosis of diabetes by screening:

1-year results from the ADDITION-Cambridge trial cohort

Abstract

Background

Uncertainties persist concerning the effects of early intensive management of type 2 diabetes and which patients benefit most from such an approach.

Aim

To describe change in modelled cardiovascular risk in the 14 months following diagnosis, and to examine which baseline patient characteristics and treatment components are associated with risk reduction.

Design and setting

A cohort of individuals from a pragmatic, single-blind, cluster-randomised controlled trial of 236 females and 361 males with screen-detected type 2 diabetes and without prior cardiovascular disease (CVD), from 49 GP surgeries in eastern England, examined at baseline (2002–2006) and after 14-months' follow-up.

Method

Multiple linear regression was used to quantify the association between baseline patient characteristics, treatment components, and change in modelled 10-year cardiovascular risk (UK Prospective Diabetes Study [UKPDS] [version 3] risk engine).

Results

There was a downward shift in the distribution of modelled CVD risk over 14 months mean 31% [standard deviation (SD) = 14%] to 26% [SD = 13%]. Older individuals, males, and those with a larger waist circumference at baseline exhibited smaller risk reductions. Individuals prescribed higher numbers of drugs over the follow-up period, and those who decreased their energy intake or reduced their weight, demonstrated larger reductions in modelled risk.

Conclusion

It is possible to achieve significant reductions in modelled CVD risk over 14 months following diagnosis of diabetes by screening. Risk reduction appeared to be driven mainly by prescription of higher numbers of drugs, decreased energy intake, and weight reduction. There was room for further risk reduction, as many patients were not prescribed recommended treatments.

Keywords

cardiovascular diseases, prevention and control; diabetes mellitus; equity; mass screening; primary care; risk factors; socioeconomic factors.

INTRODUCTION

Population-based screening and early treatment for type 2 diabetes could potentially reduce the growing public health burden of this disease.^{1,2} Several trials suggest that intensive treatment of individual risk factors is effective in those with clinically diagnosed type 2 diabetes.^{3–6} However, there is little evidence to inform the treatment of screen-detected patients. One-year results from the Dutch centre of the ADDITION-Europe trial (Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care),⁷ showed that intensive multifactorial treatment of screen-detected individuals was associated with significant reduction in cardiovascular risk factors without worsening quality of life.⁸ Nonetheless, uncertainties persist concerning the potential magnitude of risk reduction achievable in the first year after diagnosis, and the factors associated with reduction in risk.

Research suggests that practitioners might be reluctant to recommend intensive treatment to asymptomatic individuals with screen-detected diabetes.⁹ Furthermore, individuals at high risk of diabetes exhibit characteristics that have previously been associated with inequality in healthcare

provision, including low socioeconomic status,¹⁰ black and minority ethnic status,¹¹ older age,¹² and obesity.^{13,14} Social inequalities exist in the treatment of patients with coronary heart disease and diabetes.^{15–19} Evidence of specific inequities in service provision or uptake might inform the content and implementation of treatment policies in patient with early-diagnosed diabetes.

The aims of this analysis are to describe the change in modelled cardiovascular disease (CVD) risk in the first year after diagnosis in a cohort of individuals with screen-detected type 2 diabetes; explore which baseline patient characteristics and which treatment components are associated with reduction in modelled CVD risk in this screen-detected population; and assess potential variation in the provision of treatment early in the course of the disease.

METHOD

Data are presented from the ADDITION-Cambridge trial cohort. ADDITION-Cambridge is a primary-care-based study of screening for type 2 diabetes, followed by a pragmatic open-label cluster randomised controlled trial comparing intensive multifactorial treatment with routine care in patients with screen-detected diabetes. The

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How this fits in

Uncertainties persist concerning the management of diabetes early in the course of the disease. Consequently, practitioners may be reluctant to intensively treat newly-diagnosed patients identified by screening. This study shows that it is possible to achieve significant shifts in the population distribution of modelled cardiovascular disease risk, by using intensive management in the first year after diagnosis. Risk reduction appeared to be mainly driven by prescription of higher numbers of drugs, decreased energy intake, and weight reduction.

design and rationale have previously been reported.²⁰

Forty-nine general practice surgeries in the eastern region of England (26 in the intensive-treatment group [IT] and 23 in the routine-care group [RC]) recruited patients. Randomisation and screening processes have been described elsewhere.²¹ World Health Organization criteria were used to diagnose diabetes.²² All patients newly diagnosed with type 2 diabetes in the screening phase were eligible to participate in the treatment study, unless their GP indicated that they had contraindications to proposed study medication. A total of 867 eligible individuals agreed to participate.

Participants detected with type 2 diabetes were subsequently managed according to the treatment regimen to which their practice was allocated: RC or IT. RC followed the current UK national guidelines for diabetes management.²³⁻²⁵ In the IT practices, the intensification of diabetes management was achieved through the addition of a number of features to existing diabetes care.²⁰

The study aimed to educate and support GPs, practice nurses, and participants in target-driven management (using medication and promotion of healthy lifestyles) of hyperglycaemia, blood pressure, and cholesterol, based on the stepwise regimen used in the Steno-2 study.²⁶ Treatment targets and algorithms were based on trial data demonstrating the benefits of intensive treatment of cardiovascular risk factors in people with type 2 diabetes.^{4,5,26,27} Targets included glycosylated haemoglobin (HbA1c) <7.0%, blood pressure ≤135/85 mmHg, cholesterol <5 mmol/l without ischaemic heart disease or <4.5 mmol/l with ischaemic heart disease, and prescription of aspirin to those treated with antihypertensive medication.

Following publication of the Heart Protection Study,²⁸ the treatment algorithm included a recommendation to prescribe a statin to all patients with a cholesterol level ≥3.5 mmol/l.

Measurement and outcomes

Baseline and 1-year health assessments included physiological and anthropometric measures, venesection, and the completion of questionnaires. Anthropometric and clinical measures were undertaken by trained staff, following standard operating procedures. Data-collection methods have been described previously.²⁰ Standardised questionnaires were used to collect information on sociodemographic characteristics (education and social status) and lifestyle habits (smoking status). Data on medication adherence, physical activity, and dietary behaviour were collected using validated self-report questionnaires: the Medication Adherence Report Scale (MARS),²⁹ the EPIC-Norfolk physical activity questionnaire (EPAQ-2),³¹ and a food-frequency questionnaire,³¹ respectively. Individuals were considered to be 'adherent' to medication if they attained a MARS score >23/25. Information from EPAQ-2 was used to derive total physical activity and types of physical activity (expressed in metabolic equivalent hours per week). Information from the food-frequency questionnaire was used to derive total energy intake (expressed in kcal).

The primary endpoint at 1-year follow-up was the modelled 10-year risk of cardiovascular disease using the UK Prospective Diabetes Study (UKPDS) engine version 3.0. This is a diabetes-specific absolute risk-assessment tool that defines CVD as the first to occur of myocardial infarction, sudden cardiac death, other incident ischaemic heart disease, stroke, and peripheral vascular disease.

Participants with complete data on the UKPDS score variables (sex, ethnicity, smoking status, presence or absence of atrial fibrillation, systolic blood pressure, HbA1c, total cholesterol, high-density lipoprotein (HDL)-cholesterol), and without a self-reported history of macrovascular disease, were assessed. A total 736 participants completed the follow-up health assessment after a mean of 14 months (standard deviation [SD]=3.0 months); 86 individuals were excluded because they reported a previous CVD event (stroke or myocardial infarction) at follow-up, and 53 people were excluded as they did not have complete data available to calculate the CVD risk score, yielding 597 participants with complete data for analysis.

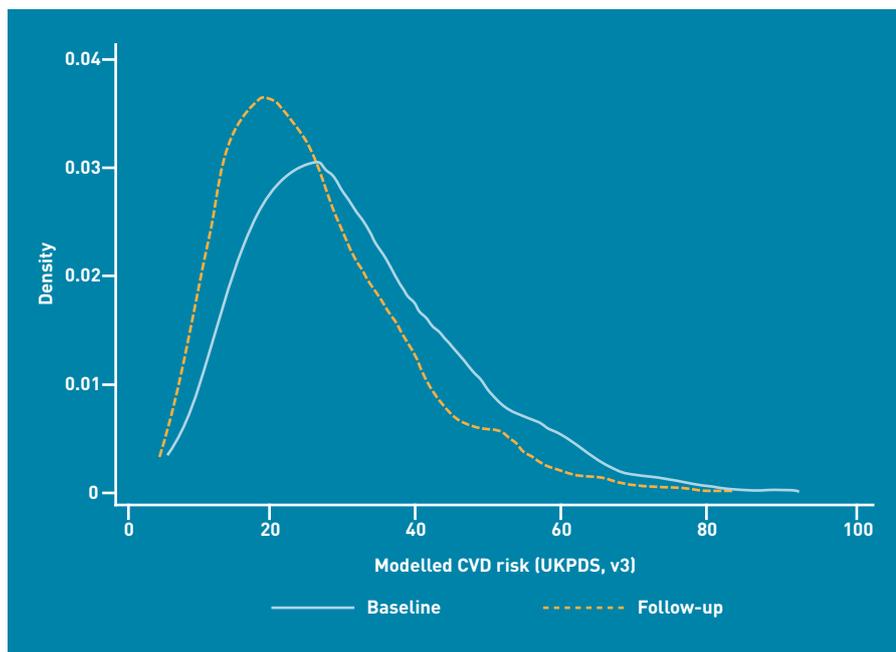


Figure 1. Distribution of 10-year modelled cardiovascular disease (CVD) risk (UKPDS risk engine, version 3) at baseline and follow-up in the ADDITION-Cambridge cohort.

Statistical analyses

A cohort analysis of ADDITION-Cambridge trial data was conducted. Change in modelled CVD risk was calculated by subtracting baseline CVD risk from follow-up CVD risk. Multiple linear regression models were used to describe the association between baseline patient characteristics, intervention components, and change in CVD risk; results are reported as unstandardised beta coefficients. All models were adjusted for baseline CVD risk and randomisation group, and took clustering by GP practice into account. The residuals of all linear

regression models were checked to ensure that they were normally distributed. Models were also run separately by trial arm and by sex. As results were largely similar, the data were pooled and results from linear regression models based on data from the whole cohort are presented. Any difference by trial arm or sex is reported. In the analysis of change in plasma vitamin C, patients who reported taking vitamin C tablets were excluded. Sensitivity analyses were conducted to examine possible differences in 10-year modelled CVD risk in participants with and without a prior CVD event at baseline. All data were analysed using STATA (version 11.0).

RESULTS

On average, modelled 10-year CVD risk declined in the whole cohort over 14 months (Figure 1). At baseline, the mean modelled CVD risk was 31.0% (SD = 14.4%), reducing to 25.7% (SD = 12.6%) at follow-up. The magnitude of the reduction in modelled CVD risk was directly related to baseline CVD risk; participants with the highest modelled risk at baseline demonstrated the biggest decrease in modelled risk, while, on average, individuals with the lowest baseline risk had the smallest change in modelled risk. Baseline patient characteristics are shown in Table 1.

Baseline patient predictors of CVD change

Female sex and Asian ethnicity were associated with a significant decrease in 10-year modelled CVD risk, while education, social class, and marital status did not demonstrate any association. Older individuals and those with a larger waist circumference at baseline were less likely to reduce their modelled risk over the year. Smoking status and body mass index (BMI) were not associated with change in modelled risk. Stratifying by intervention group showed largely similar results, with a few exceptions. High baseline BMI in the RC group was associated with a smaller change in modelled risk. The association between large baseline waist circumference and CVD risk was only present in the RC group. Male sex was associated with smaller relative reductions in modelled risk, particularly in the RC group (Table 2).

Characteristics of treatment associated with change in modelled CVD risk

Prescription of higher numbers of drugs over the follow-up period was associated with larger reductions in modelled risk (Figure 2). In particular, risk reduction was greater among patients initiated on statin

Table 1. Baseline participant characteristics in the ADDITION-Cambridge cohort, stratified by sex

Variables	Females (n = 236)	Males (n = 361)
Mean age, years (SD)	62.3 (6.1)	59.8 (7.7)
Mean 10-year CVD risk, % (SD)	22.4 (10.0)	36.6 (14.1)
Ethnicity: white, n (%)	226 (96)	353 (98)
Post-16 years full-time education, n (%)	118 (49)	180 (57)
Civil status: married, n (%)	166 (70)	294 (70)
Current smokers, n (%)	35 (15)	64 (18)
Median HbA1c, %, (IQR)	6.7 (6.3–7.6)	6.9 (6.3–8.0)
Mean blood pressure, mmHg (SD)	139.7 (19.6)	143.8 (19.4)
Systolic	79.2 (8.9)	84.2 (10.7)
Diastolic		
Mean BMI, kg/m ² (SD)	34.3 (5.8)	32.7 (5.2)
Mean waist circumference, cm (SD)	107.3 (13.1)	114.3 (13.0)
Lipids		
Mean total cholesterol, mmol/l (SD)	5.65 (1.16)	5.35 (1.03)
Median Triglycerides, mmol/l (IQR)	1.7 (1.2–2.4)	1.80 (1.3–2.6)
Mean HDL-cholesterol, mmol/l (SD)	1.32 (0.35)	1.11 (0.30)

BMI = body mass index. CVD = cardiovascular disease. HDL = high-density lipoprotein. IQR = interquartile range. SD = standard deviation.

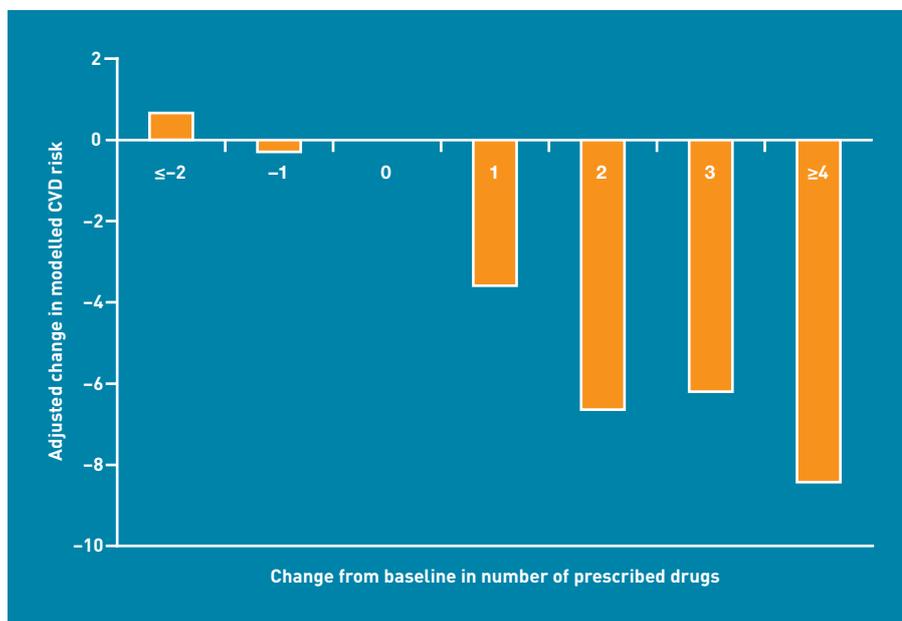
Table 2. Baseline predictors of change in modelled 10-year cardiovascular risk score (UKPDS risk engine version 3) in the ADDITION-Cambridge cohort

Variable	n (%)	Beta coefficient ^a	(95% CI)	P-value
Sex				
Female	2.36 (40)	—	—	—
Male	3.61 (60)	3.84	2.28 to 5.39	<0.01
Age at diagnosis, continuous variable				
		0.18	0.09 to 0.27	<0.01
Education, age finished, years				
<16	2.71 (45)	—	—	—
16–18	246 (41)	-0.61	-1.92 to 0.71	0.36
>18	71 (12)	-0.62	-2.64 to 1.40	0.54
Smoking				
Never	2.38 (40)	—	—	—
Former	260 (44)	1.29	-0.20 to 2.78	0.09
Current	99 (17)	0.95	-0.39 to 2.28	0.16
BMI, baseline				
		0.02	-0.08 to 0.12	0.68
Waist circumference, continuous variable				
		0.05	0.01 to 0.09	0.01
Ethnicity				
White	578 (97)	—	—	—
Asian	17 (3)	-3.20	-5.01 to -1.40	<0.001
Social class				
Professional	31 (5)	—	—	—
Managerial and technical	204 (34)	-0.32	-3.09 to 2.45	0.82
Skilled occupation: non-manual	93 (16)	-2.94	-5.93 to 0.05	0.05
Skilled occupation: manual	152 (25)	-0.01	-3.15 to 3.14	1.00
Partly skilled	68 (11)	-0.91	-3.55 to 1.72	0.49
Unskilled	38 (6)	-1.18	-4.67 to 2.32	0.50
Civil status				
Unmarried	460 (77)	—	—	—
Married	36 (6)	-2.01	-4.74 to 0.72	0.15
Divorced/separated	54 (9)	-0.77	-2.62 to 1.09	0.41
Widow/widower	45 (8)	-0.94	-1.66 to 3.54	0.47

BMI = body mass index. CVD = cardiovascular disease. CVD risk change = follow-up CVD risk — baseline CVD risk.

^aBeta-coefficients denote the association between baseline predictors and CVD risk change adjusted for baseline CVD risk, treatment group, and clustering by practice. Numbers do not add up to total due to missing data.

Figure 2. Change in modelled 10-year cardiovascular disease (CVD) risk (UKPDS risk engine version 3). CVD risk change = follow-up CVD risk — baseline CVD risk, adjusted for baseline CVD risk, treatment group, and taking cluster effect into account, in relation to change in total numbers of prescribed cardiovascular drugs from baseline to 14 months' follow-up.



and antidiabetic medication. This association was not seen for the initiation of antihypertensive therapy, nor for an increase in the number of antihypertensive drugs prescribed. Individuals who decreased their energy intake, reduced their weight, and stopped smoking demonstrated more modelled CVD risk reduction than those who did not (Table 3). There was no association between change in self-reported physical activity, change in fruit and vegetable consumption (reported as change in plasma vitamin C concentration³²), number of healthcare consultations during the previous 3 months, or self-reported medication adherence, and change in modelled risk. Results were unchanged by stratifying for treatment group and sex and when those with a prior CVD event were included.

Several patients were not prescribed medication despite elevated CVD risk factors. One hundred and twenty-seven (21%) patients had HbA1c 7% or more at follow-up but only 63 (50%) of these were prescribed medication to lower blood glucose. One hundred and thirty-two people (22%) had a total cholesterol above 5 mmol/l at follow-up but were not prescribed lipid-lowering therapy, and 67 participants (11%) were not prescribed antihypertensive treatment even though they had systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg at follow-up. Among those with elevated blood pressure and HbA1c, males were less likely to be prescribed treatment than females, with no sex difference for lipid-lowering treatment. Overall, female patients were prescribed the same number of drugs as males and reported the same change in number of drugs as males. Females had a larger decrease in weight compared to males (-4.2 kg versus -3.3 kg); 32% of females reduced their weight by more than 6 kg compared to 24% of males.

DISCUSSION

Summary

A downward shift was observed in the distribution of modelled 10-year CVD risk in the 14 months following diagnosis, in a population of patients with screen-detected type 2 diabetes in the east of England. Modelled CVD risk declined by 5.3% on average; this reduction was not restricted to participants with the highest baseline CVD risk. This is an important finding, as the overall population effect of treatment in the lead time between detection by screening and clinical diagnosis is a key determinant of the cost effectiveness of a screening

Table 3. Association between lifestyle, intervention components, and change in modelled 10-year cardiovascular disease risk (UKPDS risk engine version 3) in the ADDITION-Cambridge cohort

Variable	n (%)	Beta coefficient ^a	[95% CI]	P-value
Physical activity change, hours per week				
Total		-0.01	-0.02 to 0.01	0.24
Recreational		-0.01	-0.05 to 0.02	0.33
Vigorous		0.08	-0.17 to 0.33	0.51
Change in serum vitamin C		-0.01	-0.04 to 0.02	0.50
Smoking				
No change (never, former)	493 (80)	—	—	—
No change (smoking)	86 (14)	0.76	-0.45 to 1.97	0.21
Started	5 (1)	11.77	7.55 to 15.99	<0.001
Stopped	13 (2)	-3.38	-6.25 to -0.51	0.02
Weight change, continuous variable (kg)		0.25	0.13 to 0.37	<0.001
Energy intake, continuous variable (kcal/day)		0.12	0.03 to 0.22	0.01
Number of consultations in the last 3 months				
0	71 (12)	—	—	—
1	68 (11)	-2.2	-4.95 to 0.54	0.12
2	114 (9)	-1.73	-4.41 to 0.95	0.20
3	75 (13)	-1.28	-4.35 to 1.79	0.42
≥4	96 (16)	-1.84	-4.73 to 1.06	0.23
Medical adherence at 1 year				
General (MARS ≤23)	96 (16)	—	—	—
General (MARS >24)	453 (76)	-0.89	-2.55 to 0.76	0.28
Change in medication				
Total drug number change				
≤-2	13 (2)	0.66	-6.43 to 7.74	0.85
-1	44 (7)	-0.30	-2.71 to 2.12	0.81
0	181 (30)	—	—	—
1	132 (22)	-3.59	-5.31 to -1.86	<0.001
2	127 (21)	-6.64	-8.38 to -4.89	<0.001
3	62 (10)	-6.20	-8.54 to -3.86	<0.001
≥4	38 (6)	-8.43	-11.48 to -5.38	<0.001
Blood pressure drug change				
Never	197 (33)	—	—	—
Prescribed	94 (16)	-1.23	-3.33 to 0.88	0.25
Increased number	87 (15)	-0.29	-3.18 to 2.60	0.84
Lipid-lowering change				
Never	259 (43)	—	—	—
Prescribed	242 (41)	-5.99	-7.21 to -4.77	<0.001
Antidiabetic drugs				
Never	417 (70)	—	—	—
Prescribed	180 (30)	-3.94	-5.66 to -2.22	<0.001

CVD = cardiovascular disease. CVD risk change = follow-up CVD risk - baseline CVD risk. ^aBeta-coefficients denote the association between baseline predictors and CVD risk change adjusted for baseline CVD risk, treatment group, and clustering by practice. Numbers do not add up to total due to missing data.

programme.³³ Furthermore, the number of people with screen-detected diabetes is likely to rise following introduction of risk assessment in the NHS Health Checks programme.³⁴ CVD risk reduction was mainly driven by prescription of a higher number of drugs, weight loss, and decreased energy intake over the follow-up period. Results of the study showed some variation in treatment and CVD risk reduction by age, sex, ethnicity, and obesity status. Taken together, the results support the suggestion that earlier detection and primary care treatment reduce cardiovascular risk.

Strength and limitations

Data on both practitioner and patient behaviour were collected from ADDITION-Cambridge, which allowed examination of the association between patient characteristics, treatment components, and CVD risk reduction. Nearly half of all practices approached agreed to participate.²⁰ General practice registers typically cover 99% of all residents living in England.³⁵ As such, ADDITION-Cambridge participants were drawn from a large population-based sample, ensuring generalisability to similar settings. However, extrapolation of the results to more-deprived settings with greater ethnic diversity may be limited in light of the non-random recruitment of general practices and trial participants from a single geographical region (eastern England). While deprivation scores were broadly similar between participating practices, ADDITION practices serve fewer deprived communities than the average English practice.²¹

The study data are observational and should thus be interpreted with caution. The outcome measure was change in 10-year modelled CVD risk. While the UKPDS risk engine exhibits reasonable predictive performance,³⁶ it is not possible to be certain that the modelled CVD risk reduction seen in this cohort will translate into a reduction in hard CVD endpoints. Furthermore, the UKPDS score includes HbA1c, cholesterol, and blood pressure; medications that reduce these CVD risk factors are also likely to reduce modelled CVD risk. Measures of change in patient behaviour were calculated from self-reports of medication adherence, physical activity, and food intake, which may be subject to more error and bias than anthropometric and biochemical measures.

Comparison with existing literature

Several studies have shown that it is possible to achieve reduction in modelled CVD risk across the whole distribution of risk after clinical diagnosis of type 2 diabetes.^{3,6,37,38} The present study extends this finding to screen-detected patients. Results from the Dutch arm of the ADDITION-Europe trial support these findings, as significant reductions in several CVD risk factors were observed in both treatment groups after 1 year of follow-up.⁸

Prescribing increasing numbers of drugs to individuals with clinical diabetes has a significant impact on CVD risk reduction,^{3,38,39} a finding that may now be extended to modelled CVD risk among people with screen-detected diabetes. While

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Ethical approval

Ethical approval was granted by the Eastern Multi-Regional Ethics Committee (02/5/54).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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prescription of lipid-lowering or antidiabetic drugs was associated with CVD risk reduction in the present study cohort, prescribing or increasing antihypertensive medication was not. The risk algorithm used to select high-risk individuals for screening included antihypertensive medication as a variable; therefore, 51% of the cohort were already prescribed antihypertensive medication at baseline. Further, patients prescribed these drugs during follow-up had a larger change in unadjusted risk score than individuals who were not prescribed these drugs. This was due to high CVD risk at baseline, suggesting that the main impact of antihypertensive medication was in the higher-risk group. Increased prescribing was not associated with an increased risk of mortality or hypoglycaemic episodes, suggesting that early treatment of individuals with screen-detected diabetes does not cause harm.⁴⁰

Intensive lifestyle interventions, including promotion of physical activity, have been associated with clinically significant reductions in weight and improvements in several CVD risk factors.^{41,42} It was found in the present study that weight reduction and reduced daily energy intake, but not physical activity, were related to reduction in modelled CVD risk. Two recent studies show that weight reduction and diet may be more important than physical activity in terms of reducing hypertension and improving glycaemic control.^{35,43} However, the lack of effect of physical activity might also be explained by differential measurement error and bias; for example, changes in patient behaviour appeared to be quite small and were probably measured less precisely than, for example, prescribed medication.

Male patients were less likely to reduce their modelled CVD risk than females. No difference was found in levels of prescribed medication between males and females, but males were over-represented in groups with untreated elevated risk factors, indicating that additional risk reduction may have been possible in this group. These results are

contrary to previous findings, where females with diabetes are reported to receive less medication and have poorer control of important modifiable risk factors than males.^{17,18,44} It was also found that reductions in modelled CVD risk were less likely among older participants, despite their having a higher level of CVD risk factors. This supports previous literature, in which patients aged >65 years with CVD had a reduced chance of being prescribed statins than younger individuals in England,¹⁵ suggesting that GPs may be reluctant to intensively treat older patients. The 17 Asian participants included in the present study demonstrated a larger risk reduction than their white counterparts, indicating that practitioners might be more vigilant in the treatment of this ethnic group. However, results should be interpreted with caution given the small numbers. In the RC group, individuals with a larger waist circumference and larger BMI at baseline were less likely to reduce their CVD risk. Clinicians admit to having negative attitudes towards obese patients,¹⁴ and obese patients report discrimination and poorer treatment from health providers.^{45,46} However, this finding was not observed in the IT group, suggesting that the education of primary care teams and the use of target-driven treatment algorithms may have reduced the potential for inequity of provision of treatment.

Implications for practice

It is possible to shift the distribution of modelled CVD risk in the first year after diagnosis in a population with screen-detected type 2 diabetes treated in primary care. This risk reduction is likely to be of clinical significance and, in this study, was mainly driven by prescription of a higher number of drugs, weight loss, and decreased energy intake. There is some suggestion that males with higher CVD risk were less intensively treated than females, especially in the control group. Even in this selected trial cohort there was room for further risk reduction as many patients were not prescribed recommended treatments.

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