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# Prediabetes, participation in the English National Health Service Diabetes Prevention Programme, and associations with COVID-19-related mortality: A whole population study

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A B S T R A C T

*Aims:* To assess the effects of non-diabetic hyperglycaemia (NDH, also known as pre-diabetes), including the impact of the NHS Diabetes Prevention Programme (NHS DPP), on COVID-19-related mortality during the pandemic.
*Methods:* This study included all 61,438,225 individuals registered with General Practices in England and alive on 1st March 2020. We assessed COVID-19-related mortality in the 2,290,280(3.7 %) individuals with diagnosed NDH between March 2020 and February 2022 compared to those without diagnosed NDH or diabetes using Cox regression to adjust for demographic factors and cardiovascular comorbidities. Individuals with diagnosed NDH were further sub-categorised based on their contact with the NHS DPP (N = 376,590). Analyses were stratified by age (years) (<50, 50–69 and ≥ 70).
*Results:* There were 158,070 COVID-19 deaths; 17,280(11 %) for people with diagnosed NDH. The adjusted hazard ratio (HR) was 0.95(0.93–0.96),p < 0.001 for those with diagnosed NDH compared to those without diagnosed diabetes or NDH. By age (years), HRs were, 2.53(2.23–2.88),p < 0.001 for < 50, 1.29(1.24–1.35),p < 0.001 for 50–69 and 0.87(0.85–0.89),p < 0.001 for ≥ 70. NHS DPP attendance was associated with lower COVID-19 mortality with a dose–response relationship with engagement.
*Conclusions:* Younger people with diagnosed NDH were at higher relative risk of COVID-19 mortality. Attendance at the NHS DPP was associated with significantly lower COVID-19-related mortality.

## 1. Introduction

There is now a wealth of data published internationally linking diabetes status with more severe COVID-19 outcomes including COVID-19-related mortality [1]. However, the role of prediabetes is less clear and has not been studied to the same extent [2].

In 2016, the National Health Service (NHS) in England established the Healthier You: NHS Diabetes Prevention Programme (NHS DPP) and just over 2 years later saw England achieve universal population coverage. The NHS DPP was developed to prevent or delay the onset of type 2 diabetes, by delivering free-of-charge lifestyle interventions to adults aged 18 years and over already identified to be at high risk, defined as having nondiabetic hyperglycaemia (NDH) (HbA1c 42–47 mmol/mol [6.0– 6.4 %] or fasting plasma glucose [FPG] 5.5–6.9 mmol/L) – otherwise known as prediabetes. The rationale, justification, development and implementation of the programme and the corresponding weight loss and HbA1c reduction trajectories on programme have been described previously [3,4]. By February 2022, nearly one million people in England with NDH had been referred into the Programme and over 400,000 had attended at least one intervention session.

To support long term evaluation and monitoring of the Programme, in 2017 the National Diabetes Audit was extended to include data on all individuals in England with a code for NDH within their electronic health record [5]. Since the publication of national guidelines around the use of HbA1c for diagnosis of Type 2 diabetes and NDH in 2012 [6], there has been a shift in clinical practice such that diagnoses in England are now made in over 90 % of individuals through HbA1c testing, rather than through fasting glucose or oral glucose tolerance testing. The combination of implementation of the NHS DPP nationally with the

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introduction of financial incentives for monitoring of NDH and the regular audit of coded diagnoses in recent years have driven high levels of NDH identification and registration by general practices in England [7]. This has provided important opportunities for epidemiological study of the entity of prediabetes when assessed through HbA1c according to NDH criteria. This has also supported an independent evaluation exploiting the staged roll-out of the NHS DPP across England, demonstrating that programme-access was associated with a 7 % reduction in Type 2 diabetes incidence within populations served by the programme over the 18-month period up until March 2020 [8].

We therefore aimed to undertake a whole population study in England exploring the potential association between NDH and COVID-19-related mortality. We also aimed to assess whether participation in and completion of the NHS DPP was associated with a lower rate of COVID-19-related mortality in those with NDH during the pandemic.

## 2. Methods

### 2.1. Study design and data sources

This is a whole population study including all individuals registered with a General Practice (GP) in England and alive on 1st March 2020, assessing the risk of COVID-19-related mortality in people with diagnosed NDH compared to the general population (those without diagnosed NDH or diagnosed diabetes (Type 2 diabetes, Type 1 diabetes or other forms of diabetes)).

The Master Patient Index (MPI) was used to identify all individuals in England who were registered with a GP in England. Patient demographics, birth month and year, sex, care home status and Lower layer Super Output Area (derived from postcode of residence) are included in this dataset.

The National Diabetes Audit (NDA) was used to identify all individuals diagnosed with NDH or diabetes. The NDA was established in 2003 to assess the quality of, and variation in, diabetes clinical care and outcomes across England in individuals with a coded diganosis of diabetes. In 2017, the audit was extended to include individuals with a coded diagnosis of NDH. Since 2017/18, over 98 % of general pratices in England have provided data to the NDA. However, there is still a degree of under-coding: 813,106 individuals have been identified in England whose latest HbA1c was between 42–47 mmol/mol (6.0– 6.4 %) but were not coded as having NDH or diabetes [9].

The NHS DPP Minimum Dataset (MDS) was used to identify all individuals who had been referred to the NHS DPP. Individuals are eligible for the NHS DPP if they have a blood test within the previous 12 months indicating NDH, are 18 years of age or over, not pregnant and not previously diagnosed with diabetes. The NHS DPP delivers behavioural interventions that encourage weight loss in those who are overweight or maintenance of a healthy weight, increased physical activity and a healthier diet through at least 13 face-to-face group-based sessions over at least 9 months.

The Bridges to Health national population segmentation dataset was used to identify individuals' long-term conditions and ethnicity. The dataset incorporates more than 10 years of data from the Secondary Uses Service, a collection of data from all hospitals in England, including admitted patient care data, outpatient data, and emergency care data. The segmentation dataset includes comorbidity and ethnicity data for individuals, derived from activity occurring up to March 31, 2019, for comorbidity and Feb 28, 2020, for ethnicity.

The Quality and Outcomes Framework (QOF) was used as a surrogate to assess quality of primary care delivered to each individual and was used to identify the total points allocated in 2019/20 to the GP practice of each individual in England [10]. QOF is a voluntary pay-for-performance scheme for all GP practices in England and has been used previously as a marker of overall care quality in general practice [8].

Civil death registrations collated by the Office for National Statistics were used to identify COVID-19-related deaths and non-COVID-19-related deaths. COVID-19 deaths were identified by an ICD 10 code of U07.1 (COVID-19, virus identified), U07.2 (COVID-19, virus not identified), U09.9 (Post-COVID condition) or U10.9 (multisystem inflammatory syndrome associated with COVID-19) mentioned in any position on the death certificate.

Data is collected and used in line with NHS England's purposes as required under the statutory duties outlined in the NHS Act 2006 and Health and Social Care Act 2012. Data is processed using best practice methodology underpinned by a Data Processing Agreement between NHS England and Outcomes Based Healthcare Ltd (OBH), who produce the Segmentation Dataset on behalf of NHS England. This ensures controlled access by appropriate approved individuals, to anonymised/pseudonymised data held on secure data environments entirely within the NHS England infrastructure. Data is processed for specific purposes only, including operational functions, service evaluation and service improvement. Where OBH has processed data, this has been agreed and is detailed in a Data Processing Agreement. The data used to produce this analysis has been disseminated to NHS England under Directions issued under Section 254 of the Health and Social Care Act 2012.

### 2.2. Outcomes

The primary outcome was COVID-19-related mortality between March 2020 and February 2022.

### 2.3. Covariates

All individuals in England were assigned into one of five 'glycaemic-status' categories based on the recorded date of diagnosis of NDH or diabetes on any date prior to the 1st March 2020: NDH, type 2 diabetes (T2DM), type 1 diabetes (T1DM), other forms of diabetes (Other DM), and by exclusion, without a diagnosis of diabetes or NDH (no DM or NDH). Individuals with a recorded diagnosis of NDH were further subcategorised based on their contact with the NHS DPP: not referred to the NHS DPP; referred to the NHS DPP and did not attend an initial assessment session or any intervention sessions; referred to the NHS DPP and attended an initial assessment session and/or intervention sessions but did not complete; and referred to the NHS DPP, attended an initial assessment session and intervention sessions and completed the programme (defined as attended more than 60 % of sessions) [4]. To allow enough time for participants to finish the programme over the period of data collection, only referrals made between June 2016 and the 28th February 2021 were included in the analyses. Each individual was followed through the study period and any transitions between categories identified (note, transitions from NDH to normoglycaemia were assumed not to occur, as there are no clinical recommendations currently in England to remove such individuals from the NDH register).

Age, sex, ethnicity, and socioeconomic deprivation were identified as potential confounding factors. Age was calculated as of 1st March 2020 and grouped into 10-year age groups. Sex was recorded as male, female, or unknown. Ethnicity was classified as white, Asian, black, mixed, other, or unknown. Socioeconomic deprivation was defined by the English indices of deprivation 2019 associated with the lower layer super output area derived from the individual's home postcode and grouped into quintiles [11]. Individuals were allocated to one of the seven regions in England used for healthcare administration purposes according to their home postcode.

We also included data on admissions to hospital with cardiovascular comorbidities (coronary heart disease, cerebrovascular disease and heart failure), frailty, and whether or not individuals lived in a care home. GPs associated with each individual referred to the NHS DPP were assigned to one of three groups based on when practices began to first participate in the programme; Wave 1 (which started from June 2016), Wave 2 (from April 2017) and the Wave 3 (from April 2018) [9]. The percentage of total QOF points achieved by each GP in 2019/20 were grouped into quartiles: low (36.8 %-94.4 %), mid-low (94.41 %-97.36

%), mid-high (97.37 %-99.11 %) and high (99.12 %-100 %).

### 2.4. Statistical analyses

COVID-19 mortality rates by age group and glycaemic status were calculated. Cox regression models were used to estimate the association between glycaemic status and COVID-19-related mortality in England, adjusted for age, sex, ethnicity, deprivation quintile, and region. Non-COVID-19 related deaths were censored in the model. Diagnosed NDH was further sub-categorised based on contact with the NHS DPP. Log-log plots were created for each covariate included in the model using the Stata command "stphplot", to check the assumption of proportional hazards. To make these plots computationally feasible, they were generated for a random sample of 1.2 million individuals. There was a significant interaction between age and glycaemic status ($p < 0.001$) and therefore, analyses were stratified by age group (<50 years, 50–69 years and 70 years and over). No other interactions were investigated. Analyses were repeated also adjusting for cardiovascular comorbidities, frailty, care home status, NHS DPP wave and GP QOF performance. In sensitivity analyses, all individuals who were referred to the NHS DPP were included, irrespective of whether they had a coded diagnosis of NDH. We also assessed COVID-19-related mortality during the period March 2020 to November 2020 where COVID-19 vaccinations were not yet available. In addition, we assessed the association between glycaemic status and non-COVID-19 mortality with COVID-19-related deaths censored in the model.

Data were analysed with Stata (version 16). All data were rounded to the nearest five to protect patient confidentiality.

## 3. Results

There were 61,438,225 individuals of all ages registered with a GP in England on 1st March 2020. Of those, 2,290,280 (3.7 %) had NDH, 3,500,250 (5.7 %) had DM (3,190,005 (5.2 %) T2DM, 258,645 T1DM (0.4 %) and 51,600 (0.1 %) Other DM) and by exclusion, 55,647,695 (90.6 %) had no DM or NDH. Characteristics of the population by glycaemic status are shown in Table 1. Compared to those with no DM or NDH, individuals with NDH were older (the mean (SD) age was 66 [15] years for those with NDH vs 38 [22] years for those with no DM or NDH), there were higher proportions of women, individuals of Asian and black ethnicity, and they were more likely to have had previous admissions for CHD, stroke and heart failure. Compared to those with T2DM, individuals with NDH had lower proportions of men, individuals of Asian ethnicity and individuals from the most deprived quintile.

By 1st March 2020, 551,270 people had been identified with a HbA1c measurement between 42–47 mmol/mol and had been referred into the NHS DPP. However, 150,885 (27 %) did not have a code of NDH in their GP record, 20,550 (4 %) had converted to T2DM prior to March 2020 and were therefore included in the T2DM category and a further 3,245 (1 %) had died. This left 376,590 (68 %) individuals who had been referred to the NHS DPP with a diagnosis code of NDH by March 2020. Of those individuals, 149,850 (40 %) did not attend any intervention sessions, 81,875 (22 %) attended intervention sessions but did not complete the programme and 40,650 (11 %) attended intervention sessions and completed the programme. A further 104,215 (28 %) were still in progress on the programme as of 1st March 2020. Characteristics of individuals with NDH split by NHS DPP status are shown in Table 2: individuals who completed the programme were older, with higher proportions of white ethnicity and higher proportions from the least deprived quintile compared to those who did not attend any intervention sessions or did not complete the programme.

Of the 55,647,695 with no DM or NDH at baseline, 753,835 were recorded with NDH and 226,675 were recorded with T2DM by February 2022. Corresponding new diagnoses rates per 100,000 person-years were 689 (687–690) and 207 (206–208) respectively for NDH and T2DM. Of the 2,290,280 who were recorded with NDH at baseline, 150,765 were recorded with a diagnosis of T2DM by February 2022, with a corresponding new diagnosis rate of 3,653 (3,634–3,671) per 100,000 person-years. An additional 90,480 people were coded with NDH and referred to the NHS DPP by February 2021.

During 121,550,402 person years of follow up for all individuals, there were 158,070 COVID-19 deaths, of which 92,420 (58 %) were for people with no DM or NDH, 17,280 (11 %) were for people with NDH and 48,365 (31 %) were for people with DM (46,420 (29 %) T2DM, 1,280 (0.8 %) T1DM and 665 (0.4 %) Other DM). Crude mortality rates per 100,000 person-years were 84 (95 % CI 84–85) for those with no DM or NDH, 347 (342–352) for those who with NDH and 719 (713–726) for those with T2DM. Crude mortality rates increased with age for all groups (Fig. 1 panel a). For those aged under 70 years, rates were higher for those with NDH than those with no DM or NDH, while for those aged 70 years and over, rates were lower. Within each NDH referral subgroup, there was a dose response relationship between the degree of engagement with the NHS DPP and COVID-19 mortality such that rates were highest for those who had not been referred to the NHS DPP and lowest in those who completed the NHS DPP (Fig. 1 panel b).

Adjusted for age, sex, ethnicity, deprivation and region, compared to those with no DM or NDH, the hazard ratio for COVID-19 mortality for those with NDH was 0.95 (0.93–0.96), $p < 0.001$ (Fig. 2 panel A). In comparison, the hazard ratio for non-COVID-19 mortality for those with NDH was 0.88 (0.87–0.89). Including NHS DPP referral and attendance in the model, the hazard ratios for COVID-19 mortality compared to those with no DM or NDH were 1.01 (0.99–1.02), $p = 0.41$ for those who had not been referred to the NHS DPP, 0.80 (0.74–0.85), $p < 0.001$ for those referred to the NHS DPP but did not attend any intervention sessions, 0.59 (0.54–0.65), $p < 0.001$ for those who attended intervention sessions but did not complete and 0.37 (0.32–0.42), $p < 0.001$ for those who attended intervention sessions and completed (Fig. 3 panel A).

Among people younger than 50 years, the hazard ratio for COVID-19 mortality (NDH vs no DM or NDH) was 2.53 (2.23–2.88), $p < 0.001$ (Fig. 2, panel B). Adjusted COVID-19 mortality remained higher for all NHS DPP referral and attendance groups compared to those with no DM or NDH (Fig. 3, panel B). Among people aged between 50–69 years, the hazard ratio for those with NDH was 1.29 (1.24–1.35), $p < 0.001$ compared to those with no DM or NDH (Fig. 3, panel C). The hazard ratios remained significantly higher for those who had not been referred to the NHS DPP and for those who had been referred but not attended any intervention sessions, while there were no significant differences for those who attended intervention sessions but did not complete or for those who attended intervention sessions and completed (Fig. 3, panel C). Among people aged 70 years and over, the hazard ratio for those with NDH was 0.87 (0.85–0.89), $p < 0.001$ compared to those with no DM or NDH (Fig. 2, panel D). In this age group, the hazard ratios for all NHS DPP referral and attendance groups remained significantly lower compared to those with no DM or NDH, with hazard ratios highest for those with NDH who had not been referred to the NHS DPP and lowest for those who had attended intervention sessions and completed (Fig. 2, panel D).

By comparison, for those with T2DM, compared to those with no DM or NDH, the hazard ratio for COVID-19 mortality was 1.73 (1.71–1.75), $p < 0.001$ (Fig. 2, panel A) and by age, 5.66 (5.20–6.16), $p < 0.001$ among people younger than 50 years, 2.97 (2.89–3.05), $p < 0.001$ for people aged between 50–69 years and 1.52 (1.50–1.54), $p < 0.001$ among people aged 70 years and over.

Inclusion of the additional covariates (cardiovascular comorbidities, frailty, care home status, NHS DPP wave and GP QOF performance) slightly attenuated the association between glycaemic state and mortality (see supplementary S1).

In sensitivity analyses, all individuals who were referred to the NHS DPP were included in the analyses, irrespective of a coded diagnosis of NDH. There was little difference in the results compared to the primary analyses (see supplementary S2). We also assessed COVID-19-related mortality between March 2020 and November 2020, where COVID-19

**Table 1**
Characteristics of individuals registered with a General Practice in England on 1st March 2020, overall and by glycaemic status.

| | | Without a diagnosis of diabetes or NDH | Diagnosed NDH | Diagnosed Type 2 diabetes | Overall | Without a diagnosis of diabetes or NDH | Diagnosed NDH | Diagnosed Type 2 diabetes | Overall |
|---|---|---|---|---|---|---|---|---|---|
| | Total | 55,647,695 | 2,290,280 | 3,190,005 | 61,438,225 | 100 % | 100 % | 100 % | 100 % |
| Age | <40 | 30,913,090 | 117,490 | 103,920 | 31,255,775 | 56 % | 5 % | 3 % | 51 % |
| | 40–44 | 3,754,025 | 90,915 | 104,115 | 3,971,135 | 7 % | 4 % | 3 % | 6 % |
| | 45–49 | 3,736,865 | 131,795 | 176,525 | 4,071,105 | 7 % | 6 % | 6 % | 7 % |
| | 50–54 | 3,713,170 | 193,320 | 270,140 | 4,204,225 | 7 % | 8 % | 8 % | 7 % |
| | 55–59 | 3,353,795 | 246,430 | 353,550 | 3,980,975 | 6 % | 11 % | 11 % | 6 % |
| | 60–64 | 2,646,060 | 264,575 | 395,810 | 3,328,650 | 5 % | 12 % | 12 % | 5 % |
| | 65–69 | 2,170,865 | 278,165 | 410,820 | 2,878,195 | 4 % | 12 % | 13 % | 5 % |
| | 70–74 | 2,058,745 | 320,810 | 447,305 | 2,843,490 | 4 % | 14 % | 14 % | 5 % |
| | 75+ | 3,299,180 | 646,785 | 927,820 | 4,902,775 | 6 % | 28 % | 29 % | 8 % |
| | Unknown | 1,895 | 0 | 0 | 1,900 | 0 % | 0 % | 0 % | 0 % |
| Sex | Male | 27,596,040 | 1,096,300 | 1,782,945 | 30,647,115 | 50 % | 48 % | 56 % | 50 % |
| | Female | 28,050,885 | 1,193,970 | 1,407,055 | 30,790,320 | 50 % | 52 % | 44 % | 50 % |
| | Unknown | 770 | 5 | 10 | 790 | 0 % | 0 % | 0 % | 0 % |
| Ethnicity | Asian | 3,169,925 | 200,680 | 382,590 | 3,769,430 | 6 % | 9 % | 12 % | 6 % |
| | Black | 1,623,905 | 94,370 | 140,240 | 1,867,725 | 3 % | 4 % | 4 % | 3 % |
| | Mixed | 890,405 | 17,865 | 25,435 | 937,235 | 2 % | 1 % | 1 % | 2 % |
| | Other | 1,520,630 | 60,110 | 84,780 | 1,671,685 | 3 % | 3 % | 3 % | 3 % |
| | White | 35,976,690 | 1,665,900 | 2,249,075 | 40,147,405 | 65 % | 73 % | 71 % | 65 % |
| | Unknown | 12,466,135 | 251,355 | 307,885 | 13,044,745 | 22 % | 11 % | 10 % | 21 % |
| Deprivation | IMD 1 (most deprived) | 11,427,970 | 482,670 | 781,555 | 12,757,040 | 21 % | 21 % | 25 % | 21 % |
| | IMD 2 | 11,570,910 | 471,350 | 715,365 | 12,821,720 | 21 % | 21 % | 22 % | 21 % |
| | IMD 3 | 11,150,675 | 466,030 | 637,760 | 12,317,640 | 20 % | 20 % | 20 % | 20 % |
| | IMD 4 | 10,812,480 | 444,045 | 566,980 | 11,884,040 | 19 % | 19 % | 18 % | 19 % |
| | IMD 5 (least deprived) | 10,638,965 | 424,505 | 486,205 | 11,607,025 | 19 % | 19 % | 15 % | 19 % |
| | Unknown | 46,695 | 1,680 | 2,145 | 50,760 | 0 % | 0 % | 0 % | 0 % |
| Region | East of England | 6,311,835 | 208,545 | 337,530 | 6,895,585 | 11 % | 9 % | 11 % | 11 % |
| | London | 9,272,320 | 380,255 | 513,655 | 10,206,465 | 17 % | 17 % | 16 % | 17 % |
| | Midlands | 10,222,415 | 390,845 | 644,005 | 11,316,335 | 18 % | 17 % | 20 % | 18 % |
| | North East & Yorkshire | 7,893,335 | 344,800 | 484,745 | 8,770,825 | 14 % | 15 % | 15 % | 14 % |
| | North West | 6,654,185 | 364,750 | 398,780 | 7,454,415 | 12 % | 16 % | 13 % | 12 % |
| | South East | 8,347,785 | 306,180 | 423,255 | 9,123,210 | 15 % | 13 % | 13 % | 15 % |
| | South West | 5,221,035 | 231,060 | 289,745 | 5,774,880 | 9 % | 10 % | 9 % | 9 % |
| | Unknown | 1,724,785 | 63,845 | 98,290 | 1,896,510 | 3 % | 3 % | 3 % | 3 % |
| CHD | Yes | 1,214,565 | 318,830 | 596,010 | 2,155,345 | 2 % | 14 % | 19 % | 4 % |
| | No | 54,433,130 | 1,971,450 | 2,593,995 | 59,282,880 | 98 % | 86 % | 81 % | 96 % |
| Stroke | Yes | 591,510 | 107,350 | 206,600 | 915,665 | 1 % | 5 % | 6 % | 1 % |
| | No | 55,056,185 | 2,182,935 | 2,983,410 | 60,522,560 | 99 % | 95 % | 94 % | 99 % |
| Heart Failure | Yes | 344,915 | 84,485 | 193,400 | 631,280 | 1 % | 4 % | 6 % | 1 % |
| | No | 55,302,775 | 2,205,795 | 2,996,610 | 60,806,945 | 99 % | 96 % | 94 % | 99 % |
| Frailty | Yes | 340,570 | 66,275 | 152,555 | 565,915 | 1 % | 3 % | 5 % | 1 % |
| | No | 55,307,125 | 2,224,010 | 3,037,450 | 60,872,310 | 99 % | 97 % | 95 % | 99 % |
| Care home | Yes | 217,025 | 26,520 | 55,285 | 301,565 | 0 % | 1 % | 2 % | 0 % |
| | No | 55,430,670 | 2,263,760 | 3,134,720 | 61,136,660 | 100 % | 99 % | 98 % | 100 % |
| QOF performance | Low (36.8–94.4) | 12,908,520 | 447,160 | 725,825 | 14,152,345 | 23 % | 20 % | 23 % | 23 % |
| | Average-low (94.41–97.36) | 14,648,045 | 573,005 | 823,465 | 16,124,765 | 26 % | 25 % | 26 % | 26 % |
| | Average-high (97.37–99.11) | 14,223,635 | 619,675 | 823,685 | 15,747,120 | 26 % | 27 % | 26 % | 26 % |
| | High (99.12–100) | 13,754,920 | 648,520 | 814,055 | 15,296,210 | 25 % | 28 % | 26 % | 25 % |
| | Unknown | 112,575 | 1,915 | 2,980 | 117,785 | 0 % | 0 % | 0 % | 0 % |
| NHS DPP Wave | Wave 1 | 28,539,825 | 1,144,695 | 1,587,480 | 31,426,085 | 51 % | 50 % | 50 % | 51 % |
| | Wave 2 | 13,955,525 | 557,645 | 792,100 | 15,383,435 | 25 % | 24 % | 25 % | 25 % |
| | Wave 3 | 13,152,345 | 587,940 | 810,430 | 14,628,705 | 24 % | 26 % | 25 % | 24 % |

**Table 2**
Characteristics of individuals coded with NDH as of March 2020 by NHS DPP status.

| | | Not referred to the NHS DPP by March 2020 | Referred to the NHS DPP and in progress | Discharged from the NHS DPP – referral only | Discharged from the NHS DPP – not completed | Discharged from the NHS DPP – completed | Not referred to the NHS DPP by March 2020 | Referred to the NHS DPP and in progress | Discharged from the NHS DPP – referral only | Discharged from the NHS DPP – not completed | Discharged from the NHS DPP – completed |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | 1,913,690 | 104,215 | 149,850 | 81,875 | 40,650 | 100 % | 100 % | 100 % | 100 % | 100 % |
| Age | <40 | 99,385 | 4,690 | 9,670 | 3,355 | 385 | 5 % | 5 % | 6 % | 4 % | 1 % |
| | 40–44 | 73,935 | 4,560 | 8,520 | 3,355 | 550 | 4 % | 4 % | 6 % | 4 % | 1 % |
| | 45–49 | 108,340 | 6,200 | 11,645 | 4,660 | 950 | 6 % | 6 % | 8 % | 6 % | 2 % |
| | 50–54 | 159,145 | 9,320 | 16,045 | 7,000 | 1,805 | 8 % | 9 % | 11 % | 9 % | 4 % |
| | 55–59 | 202,780 | 12,360 | 19,020 | 9,040 | 3,225 | 11 % | 12 % | 13 % | 11 % | 8 % |
| | 60–64 | 217,690 | 13,830 | 18,555 | 9,945 | 4,555 | 11 % | 13 % | 12 % | 12 % | 11 % |
| | 65–69 | 226,990 | 15,275 | 17,460 | 11,135 | 7,305 | 12 % | 15 % | 12 % | 14 % | 18 % |
| | 70–74 | 263,880 | 16,965 | 17,940 | 12,595 | 9,425 | 14 % | 16 % | 12 % | 15 % | 23 % |
| | 75+ | 561,545 | 21,010 | 30,995 | 20,785 | 12,445 | 29 % | 20 % | 21 % | 25 % | 31 % |
| | Unknown | – | – | – | – | – | 0 % | 0 % | 0 % | 0 % | 0 % |
| Sex | Male | 923,855 | 46,885 | 70,070 | 37,005 | 18,490 | 48 % | 45 % | 47 % | 45 % | 45 % |
| | Female | 989,830 | 57,330 | 79,785 | 44,870 | 22,160 | 52 % | 55 % | 53 % | 55 % | 55 % |
| | Unknown | 5 | – | – | – | – | 0 % | 0 % | 0 % | 0 % | 0 % |
| Ethnicity | Asian | 155,870 | 11,075 | 21,485 | 9,600 | 2,655 | 8 % | 11 % | 14 % | 12 % | 7 % |
| | Black | 71,900 | 6,475 | 8,465 | 5,545 | 1,980 | 4 % | 6 % | 6 % | 7 % | 5 % |
| | Mixed | 14,140 | 1,060 | 1,515 | 870 | 280 | 1 % | 1 % | 1 % | 1 % | 1 % |
| | Other | 47,680 | 3,225 | 5,585 | 2,655 | 970 | 2 % | 3 % | 4 % | 3 % | 2 % |
| | White | 1,410,570 | 72,140 | 95,175 | 56,655 | 31,360 | 74 % | 69 % | 64 % | 69 % | 77 % |
| | Unknown | 213,530 | 10,245 | 17,630 | 6,555 | 3,395 | 11 % | 10 % | 12 % | 8 % | 8 % |
| Deprivation | IMD 1 (most deprived) | 407,790 | 17,910 | 34,345 | 17,460 | 5,165 | 21 % | 17 % | 23 % | 21 % | 13 % |
| | IMD 2 | 393,895 | 19,740 | 33,360 | 17,055 | 7,300 | 21 % | 19 % | 22 % | 21 % | 18 % |
| | IMD 3 | 390,805 | 21,415 | 29,355 | 15,955 | 8,495 | 20 % | 21 % | 20 % | 19 % | 21 % |
| | IMD 4 | 370,990 | 21,670 | 26,475 | 15,465 | 9,445 | 19 % | 21 % | 18 % | 19 % | 23 % |
| | IMD 5 (least deprived) | 348,720 | 23,435 | 26,225 | 15,895 | 10,230 | 18 % | 22 % | 18 % | 19 % | 25 % |
| | Unknown | 1,495 | 40 | 90 | 40 | 15 | 0 % | 0 % | 0 % | 0 % | 0 % |
| Region | East of England | 165,945 | 11,275 | 18,480 | 7505 | 5340 | 9 % | 11 % | 12 % | 9 % | 13 % |
| | London | 308,735 | 18,680 | 30,460 | 15,870 | 6510 | 16 % | 18 % | 20 % | 19 % | 16 % |
| | Midlands | 321,845 | 18,135 | 30,000 | 13,965 | 6900 | 17 % | 17 % | 20 % | 17 % | 17 % |
| | North East & Yorkshire | 297,020 | 12,345 | 17,975 | 11,705 | 5755 | 16 % | 12 % | 12 % | 14 % | 14 % |
| | North West | 320,270 | 11,600 | 13,355 | 13,040 | 6480 | 17 % | 11 % | 9 % | 16 % | 16 % |
| | Eouth East | 244,975 | 16,110 | 28,785 | 10,875 | 5435 | 13 % | 15 % | 19 % | 13 % | 13 % |
| | South West | 201,770 | 13,310 | 6500 | 6410 | 3070 | 11 % | 13 % | 4 % | 8 % | 8 % |
| | Unknown | 53,125 | 2755 | 4300 | 2505 | 1160 | 3 % | 3 % | 3 % | 3 % | 3 % |
| CHD | Yes | 269,130 | 12,965 | 18,660 | 12,165 | 5915 | 14 % | 12 % | 12 % | 15 % | 15 % |
| | No | 1,644,560 | 91,250 | 131,190 | 69,710 | 34,735 | 86 % | 88 % | 88 % | 85 % | 85 % |
| Stroke | Yes | 93,265 | 3470 | 5710 | 3425 | 1480 | 5 % | 3 % | 4 % | 4 % | 4 % |
| | No | 1,820,425 | 100,745 | 144,145 | 78,450 | 39,165 | 95 % | 97 % | 96 % | 96 % | 96 % |
| Heart Failure | Yes | 73,770 | 2675 | 4245 | 2630 | 1165 | 4 % | 3 % | 3 % | 3 % | 3 % |
| | No | 1,839,920 | 101,540 | 145,610 | 79,245 | 39,485 | 96 % | 97 % | 97 % | 97 % | 97 % |
| Frailty | Yes | 60,060 | 1305 | 2770 | 1630 | 510 | 3 % | 1 % | 2 % | 2 % | 1 % |
| | No | 1,853,630 | 102,910 | 147,085 | 80,245 | 40,140 | 97 % | 99 % | 98 % | 98 % | 99 % |
| Care home | Yes | 25,645 | 85 | 575 | 190 | 30 | 1 % | 0 % | 0 % | 0 % | 0 % |
| | No | 1,888,045 | 104,130 | 149,275 | 81,685 | 40,620 | 99 % | 100 % | 100 % | 100 % | 100 % |
| QOF performance | Low (36.8–94.4) | 374,555 | 19,815 | 29,575 | 16,190 | 7020 | 20 % | 19 % | 20 % | 20 % | 17 % |
| | Average-low (94.41–97.36) | 476,080 | 26,305 | 39,380 | 21,185 | 10,060 | 25 % | 25 % | 26 % | 26 % | 25 % |

(*continued on next page*)

**Table 2** (*continued*)

| | | Not referred to the NHS DPP by March 2020 | Referred to the NHS DPP and in progress | Discharged from the NHS DPP – referral only | Discharged from the NHS DPP – not completed | Discharged from the NHS DPP – completed | Not referred to the NHS DPP by March 2020 | Referred to the NHS DPP and in progress | Discharged from the NHS DPP – referral only | Discharged from the NHS DPP – not completed | Discharged from the NHS DPP – completed |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average-high (97.37–99.11) | 517,775 | 28,545 | 39,610 | 21,970 | 11,775 | 27 % | 27 % | 26 % | 27 % | 29 % |
| | High (99.12–100) | 543,745 | 29,475 | 41,120 | 22,430 | 11,745 | 28 % | 28 % | 27 % | 27 % | 29 % |
| | Unknown | 1530 | 75 | 170 | 95 | 45 | 0 % | 0 % | 0 % | 0 % | 0 % |
| NHS DPP Wave | Wave 1 | 924,460 | 51,130 | 97,410 | 47,170 | 24,525 | 48 % | 49 % | 65 % | 58 % | 60 % |
| | Wave 2 | 464,605 | 26,485 | 30,855 | 24,000 | 11,700 | 24 % | 25 % | 21 % | 29 % | 29 % |
| | Wave 3 | 524,620 | 26,605 | 21,590 | 10,700 | 4420 | 27 % | 26 % | 14 % | 13 % | 11 % |

vaccinations were not yet available. Results were broadly similar to the primary analyses (see supplementary S3 and S4). Log-log plots provided reassurance that there were no major violations of the proportional hazard assumption.

## 4. Discussion

For the first time internationally, we describe the risk of COVID-19-related mortality in people with NDH at whole population level. While overall, the hazard of COVID-19-related mortality for those with NDH was slightly lower than those with no DM or NDH, for younger age groups, NDH was associated with increased COVID-19-related mortality. Furthermore, if we exclude those who have had contact with the DPP then there is no difference in the hazard of COVID-19-related mortality for those with NDH compared to those with no DM or NDH.

In the subgroup of those with NDH referred to the NHS DPP, attendance at the NHS DPP was associated with significantly lower rates of COVID-19-related mortality, with a demonstrable dose–response relationship. While we have found higher rates of COVID-19-related mortality in those with NDH up to the age of 70 years, the mortality benefits associated with programme participation were apparent in those over this age threshold, suggesting that some of the COVID-19 mortality benefit attributable to programme participation may be related to factors other than glycaemic status. Indeed, this may relate to weight loss, or other factors related to the lifestyle intervention.

A number of studies have reported on the role of prediabetes and more severe COVID-19 outcomes, including COVID-19 mortality. A retrospective cohort study from Japan including 2,430 patients, reported that prediabetes was a risk factor for critical COVID-19 outcomes, and that HbA1c in those with prediabetes was associated with COVID-19 severity [12]. A Mexican study including 317 patients, reported similar findings [13]. A systematic review and *meta*-analysis including only 3,027 people, highlighted high heterogeneity between studies, and reported that prediabetes was significantly associated with adverse outcomes of COVID-19 with an odds ratio of 2.58 (95 %CI, 1.46–4.56) [14]. A population-based study in Israel reported pre-infection fasting glucose values within the prediabetes range to be associated with increased risk for severe COVID-19 in those testing positive [15]. A retrospective observational study applying USA data from electronic health records suggested that metformin was associated with reduced COVID-19 severity in people with prediabetes [16].

As of 1st March 2020, there were 2,290,280 individuals recorded and diagnosed with NDH on GP registers in England, corresponding to a prevalence 3.7 %. In 2015, Public Health England estimated there were 5 million adults in England with NDH [17]. This suggests that around 46 % of people with NDH have been diagnosed and are included on GP registers, with those undiagnosed, included in the group 'with no DM or NDH'. A previous study estimated the prevalence of 'prediabetes' in England and found it to be significantly higher than the PHE estimates, at 35 % [18]. However, this was estimated using the American Diabetes Association definition of prediabetes, which uses a much broader HbA1c definition of 39–47 mmol/mol, whereas the PHE estimate, in-line with this study, uses 42–47 mmol/mol.

Numerous studies have demonstrated a link between diabetes status and COVID-19-related mortality [1]. A previous population-based study in England assessed the risk of COVID-19 mortality over the first 72 days of the pandemic in 2020 and reported an adjusted odds ratio of 2.03 (1.97–2.09) in people with type 2 diabetes compared to those without diabetes with a greater effect observed at younger ages, similar to the corresponding adjusted hazard ratios reported here [19]. A systematic review of 18 studies, reported a relative risk of 2.11 (1.40–3.19) for severe COVID-19 in people with diabetes compared to those without [20]. Another population-based study in England, assessed associations between risk factors and COVID-19 mortality in people with type 1 and type 2 diabetes [21]). Male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation and previous stroke and heart

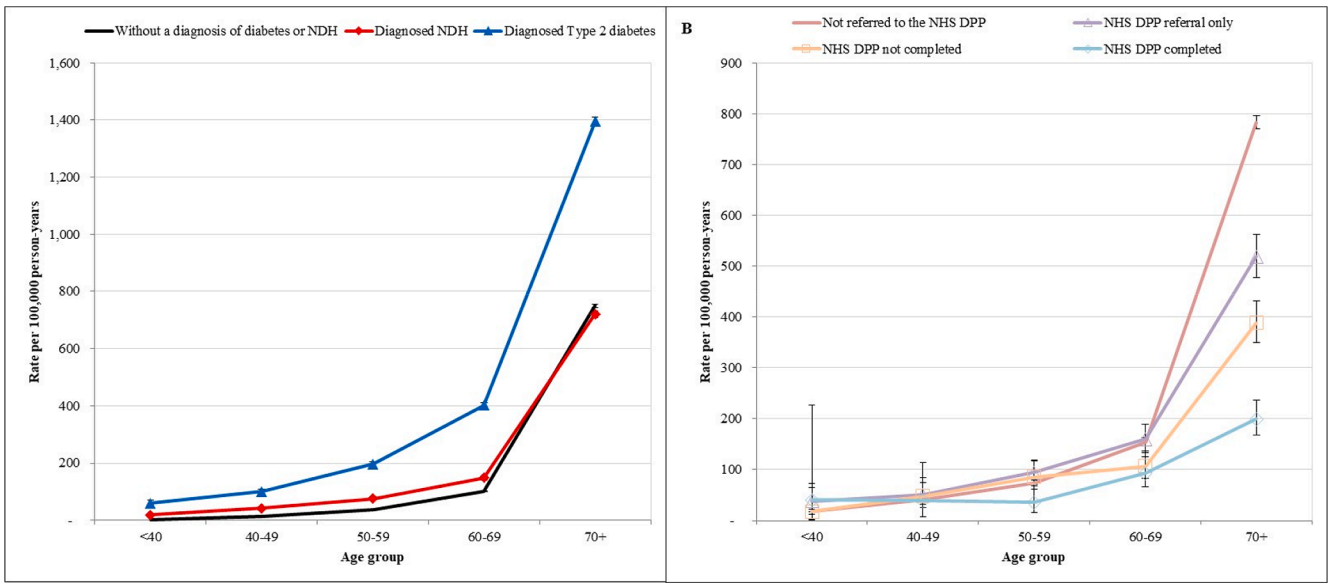


**Fig. 1.** COVID-19 mortality rates per 100,000 person-years from Mar 2020 to Feb 2022 by age group and glycaemic status (panel A), among those with NDH split by NHS DPP status (panel B).

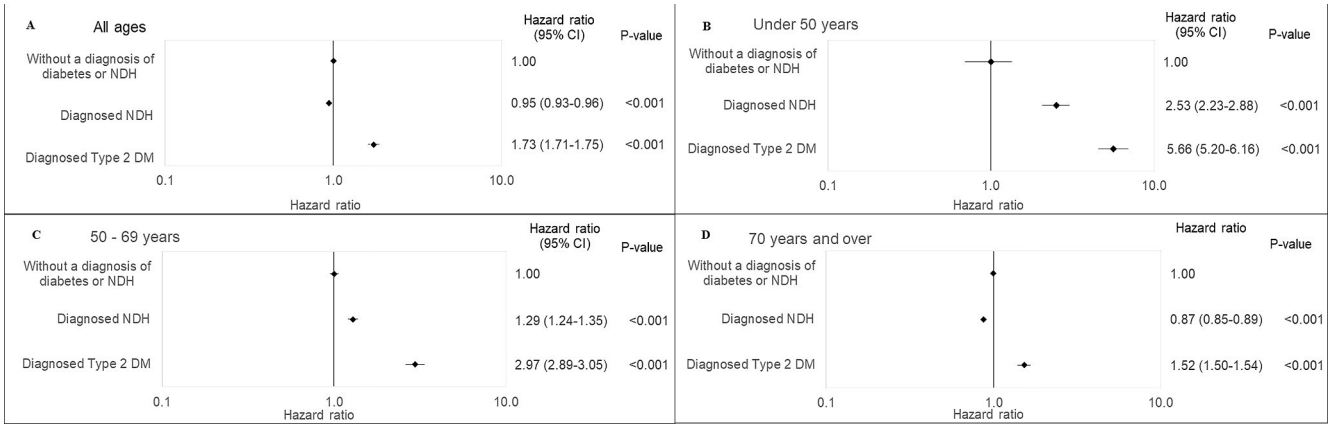


**Fig. 2.** Hazard ratios for COVID-19 mortality by glycaemic state for all ages (panel A) and by age group: under 50 years (panel B), 50–69 years (panel C) and 70 years and over (panel D) *Hazard ratios estimated using Cox regression adjusted for age, sex, ethnicity, deprivation and region.

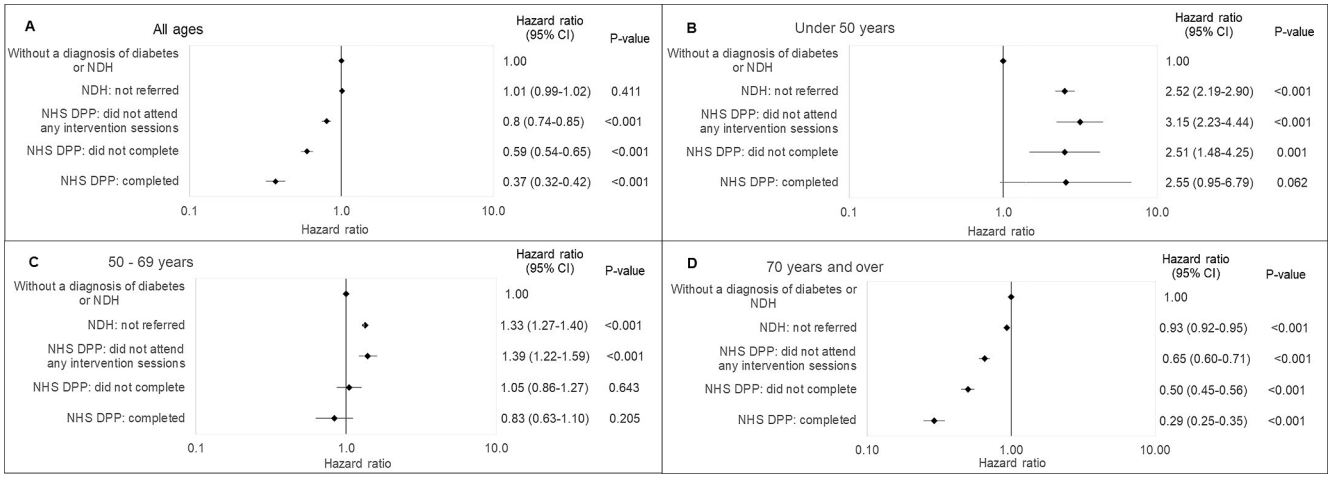


**Fig. 3.** Hazard ratios for COVID-19 mortality for those with NDH split by NHS DPP status for all ages (panel A) and by age group: under 50 years (panel B), 50–69 years (panel C) and 70 years and over (panel D) *Hazard ratios estimated using Cox regression adjusted for age, sex, ethnicity, deprivation and region.

failure were associated with increased COVID-19 mortality. Compared with people with an HbA1c of 48–53 mmol/mol, people with type 2 diabetes with a HbA1c >=59 mmol/mol or < 48 mmol/mol had significantly higher COVID-19 mortality rates. Compared to people with a BMI of 25–29.9, people with type 2 diabetes with a BMI > 35 kg/m2 or < 25 kg/m2 had significantly higher COVID-19 mortality rates [21].

A major strength of this study is its size, covering 61,438,225 people: almost the entire population of England. However, we were only able to adjust for three cardiovascular comorbidities (coronary heart disease, cerebrovascular disease and heart failure) and were unable to adjust for other comorbidities, most notably, hypertension and chronic kidney disease, due to incomplete recording in the hospital-derived datasets used. Likewise, we were also unable to adjust for BMI and smoking status due to limitations in the datasets used. In addition, only data regarding cardiovascular comorbidities up to the end of March 2019 were used. Therefore, a small proportion of the population for whom cardiovascular comorbidities were first recorded after April 2019, will have been misclassified. While we were also unable to adjust for COVID-19 vaccination status, we did assess the period March 2020 to November 2020 where COVID-19 vaccinations were not yet available, and the results were broadly similar to the primary analyses. However, it is also possible that the benefits of early vaccination in elderly individuals with NDH may have contributed to the findings in the primary analyses.

This study assesses observational data collected during routine care delivery, without randomisation of participation in the NHS DPP. While we have taken account of a number of measured confounders in our regression models, there will be other unmeasured confounders. It is therefore not possible to disentangle how much of the COVID-19 mortality benefits are a direct consequence of the lifestyle intervention, and how much are related to the characteristics of those more likely to choose to both attend and complete such an intervention. While there was no significant difference in COVID-19 mortality for those with NDH who were not referred to the NHS DPP compared to those with no DM or NDH, there was a 20 % reduction for those with NDH who were referred but did not attend any intervention sessions. While this may relate to behaviour change following their NDH diagnosis and subsequent referral to the NHS DPP, it seems unlikely to be the primary explanation, which may instead relate to the observational nature of the data and residual confounding.

This study assesses those who have been diagnosed and recorded on GP registers with NDH or diabetes. Given the asymptomatic nature of NDH and T2DM and the large numbers of individuals with undiagnosed NDH, there is a potential for misclassification which may affect outcomes for both the 'with no DM or NDH' group and the NDH group. It is possible therefore, that our finding of a lower risk for people with prediabetes may be partly attributable to this misclassification in addition to unmeasured confounders. A recent study of 5,701 adults aged 66–90 years found that while long-standing diabetes had a substantial effect on short-term mortality, individuals with prediabetes remained at low risk [22]. While this study assessed all-cause mortality rather than COVID-19 mortality, we did show similar findings for non-COVID-19 mortality in our analyses.

While randomised controlled trials of diabetes prevention lifestyle interventions have been shown to reduce Type 2 diabetes incidence [23,24], and in the few cohorts that have been followed for many years, to reduce mortality [25], this is the first study to demonstrate an association between diabetes prevention programme intervention participation, and reduced COVID-19-related mortality. However, the observational nature of this subgroup does not permit us to conclude causality, and indeed unmeasured confounders may have accounted for much of the differences in rates of COVID-19-related mortality between the groups. The association between NDH and COVID-19-related mortality is complex, involving a significant interaction with age. We have shown in our whole-population data that NDH is a risk factor for COVID-19-related mortality in younger people under the age of 70 years. The apparent protective effect of NDH for COVID-19-related mortality in those 70 years of age or older may relate to reverse causality, whereby those losing weight due to other conditions that also predispose to COVID-19-related mortality, are more likely to be normoglycemic.

In conclusion, we have shown that younger people with NDH were at higher risk of COVID-19 mortality compared to those with no DM or NDH and in the subgroup of those with NDH who were referred to the NHS DPP, attendance was associated with significantly lower COVID-19-related mortality with a demonstrable dose–response relationship. These findings add to emerging evidence suggesting that adverse outcomes associated with pre-diabetes status, including in this case COVID-19-related mortality, are significant in younger, but not necessarily older, people. However, the potential for misclassification for those with undiagnosed or unrecorded NDH means that it is possible that our finding of a lower risk for older people with prediabetes may be partly attributable to this misclassification, in addition to residual confounding. Due to the observational nature of the data, it is not possible to determine the extent to which reduced COVID-19 mortality rates were a direct consequence of the NHS DPP as opposed to being related to the characteristics of those more likely to attend and complete such an intervention.

## CRediT authorship contribution statement

**Emma Barron:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Stephen J. Sharp:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis. **Kamlesh Khunti:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Chirag Bakhai:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Nicholas J. Wareham:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Jonathan Valabhji:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [JV was the National Clinical Director for diabetes and obesity at NHS England from April 2013 to September 2023 and is supported by the North West London NIHR Applied Research Collaboration and the Imperial NIHR Biomedical Research Centre. JV and EB receive funding from CW+, the official charity of Chelsea and Westminster Hospital NHS Foundation Trust. CB is an adviser to the NHS Diabetes Programme. KK has been a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme; has received grants in support of investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Pfizer, and Boehringer Ingelheim; has served on advisory boards for Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme; and is supported by the UK National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands and the NIHR Leicester Biomedical Research Centre. NW is supported by the Medical Research Council (grant MC_UU_00006/1). All other authors declare no competing interests].

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111692.

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