The adverse impact of COVID-19 pandemic on cardiovascular disease prevention and management in England, Scotland and Wales: A population-scale analysis of trends in medication data

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Abstract.

Cardiovascular disease (CVD) remains the most common cause of mortality and morbidity worldwide, yet the impact of the COVID-19 pandemic on CVD and its risk factors remains unstudied. We use medication data to proxy CVD management using routinely collected anonymised individual-level data comprising 1.32 billion records of linked community dispensed CVD medications from England, Scotland and Wales between April 2018 and July 2021. We describe monthly prevalent and incident counts, annual monthly percentage change of medicines dispensed by CVD indications, focusing on hypertension, hypercholesterolaemia, diabetes, and use interrupted time-series analysis to model the impact of the pandemic. A decline in medicines used for CVD prevention was observed with 733,586 (95%CI 516,763 to 950,409) fewer individuals initiating antihypertensive treatment than expected. This could result in 20,399 additional CVD events, including 3,406 myocardial infarctions (MIs) and 5,188 strokes, should individuals remain untreated over their lifecourse. Incident use of lipid-lowering medicines decreased by 41,456 (95%CI 31,106 to 51,805) patients per month compared to the predicted pre-pandemic trend. Use of incident medicines to treat type-2 diabetes (T2DM) decreased by approximately 12,287 (95%CI 7,686 to 16,887) patients per month. Methods to identify and treat individuals who have missed treatment and remain undiagnosed are urgently required to avoid large numbers of additional future CVD events, further adding to the indirect impacts of the COVID-19 pandemic.

219 words

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Introduction

Cardiovascular disease (CVD) remains the most common cause of mortality and morbidity worldwide; it is therefore vital to understand the impact of the COVID-19 pandemic on CVD and its risk factors. In the UK, strategies for CVD prevention include screening for health conditions and risk factors that can be modified through medication, including Type-2 diabetes (T2DM), hypertension, hypercholesterolaemia, and atrial fibrillation (AF). When adequately controlled, such measures reduce the level of CVD in the population.

The COVID-19 pandemic has disrupted health care in multiple ways, putting additional pressure on both primary and secondary care services[1-4]. How these have impacted on screening and treatment of common risk factors, including CVD risk factors, and the downstream impact of missed detection of risk factors in terms of CVD outcomes including myocardial infarction (MI) and stroke remains under studied at a national level[5].

Medicines are a key public health intervention, particularly in preventing and controlling long-term health conditions. Examining the change in the prescribed and dispensed medicines used to treat CVD risk factors over the course of the COVID-19 pandemic can be used to assess the impact on future CVD events of not treating these risk factors. This approach is complementary to studying reduction in the level of disease diagnoses and risk factor control (which is harder to track given reductions in testing during the pandemic) and so medicine changes may provide a closer representation of the real-world control (or lack thereof) of CVD risk factors within the population, following the patient pathway from diagnosis, through prescription, to dispensing of medication, to the treatment of the condition. In this study, we investigate the impact of the COVID-19 pandemic on non-COVID harm in eleven sub-populations, specifically the management of CVD defined by medicines. By highlighting monthly trends in first (incident) medication use, we can understand changes in the rate of identification of actionable CVD risk factors and unmet control within individuals due to the pandemic. The UK has comprehensive national medical records which can track health over the life course and using this we report, for the first time across >60M people in England, Scotland and Wales how a data-informed medicines-based treatment approach can provide precise and comprehensive quantification of the reduction in the treatment of CVD risk factors due to the pandemic. We believe our work has relevance for many countries given statins and antihypertensives are cheap and the mainstay of atherosclerotic CVD (ASCVD) prevention worldwide.

Methods

Data

We studied anonymised individual-level population-scale data from England, Scotland and Wales accessed through the respective national Trusted Research Environments (TREs), i.e. NHS Digital's TRE for England (referred to throughout as 'the English TRE'), the Scottish National Safe Haven and the SAIL Databank. Motivated by the public health importance of understanding the relationship between COVID-19 and CVD, the Health Data Research UK (HDR UK) British Heart Foundation (BHF) Data Science Centre (DSC) established the CVD-COVID-UK consortium and related research programme[6,7]. Through this partnership, linked, nationally-collated electronic health record (EHR) data for the population of England, Scotland and Wales have been made available to support research into the impacts of CVD on COVID-19 and vice versa. Details of the collaboration and the data included within each of the national TREs are described in full elsewhere https://www.bmj.com/content/373/bmj.n826[8]. Data processing details for this work are available under an open source license at https://github.com/BHFDSC/CCU014_01.

England

Medication data are available from a number of sources within the English TRE. First, the NHS Business Service Authority (NHSBSA) dispensing data are updated on a monthly basis and include prescriptions for all medicines dispensesd in the community in England[9]. Second, prescribing data are available within the General Practice Extraction Service (GPES) extract Data for Pandemic Planning and Research (GDPPR), including data from 98% of all English general practices. These medicines include those *a priori* selected by the CVD-COVID-UK programme predominently for their relevance to CVD and its risk factors (e.g. antihypertensive, cholesterol lowering, diabetes, antiplatelet/ anticoagulant)[8]. These prescribing data include the exact date of prescription for each drug item. The English TRE also provides data for some secondary care Electronic Prescribing and Medicines Administration (EPMA), but these are not included in the current analyses as most medicines to prevent and treat CVD are accounted for by primary care prescribing.

Scotland
The medicines data available within the Scottish National Safe Haven[10,11] come from the Prescribing Information System (PIS), which captures all prescriptions dispensed in the community in Scotland[12]. These prescriptions originate mainly from general practitioners, although other health care professionals (e.g. dentists, pharmacists) may also issue prescriptions. PIS uses a drug categorisation system based on the British National Formulary (BNF; a dictionary of descriptions and codes which represent medicines and devices used across the NHS) with the majority of the data coming through community pharmacies via the Data Capture Validation Pricing (DCVP) system. Both paper and electronic prescriptions are provided as part of Scotland's eHealth strategy. The data is updated monthly in the Safe Haven. The exact date of prescribing is available in PIS; but since PIS only captures prescriptions that have been dispensed the focus here is on Scottish dispensing data.

Wales
Primary care prescribing and dispensing data for the population of Wales are available from two main data sources within the Secure Anonymised Information Linkage (SAIL) Databank[13,14]. Firstly, prescribing data from approximately 80% of all Wales general practices are available within the Welsh Longitudinal General Practice (WLGP) data, which is updated on a monthly basis[15]. These data include the exact date of prescription for each drug item and are coded using Read codes. Secondly, dispensing data from all community pharmacies in Wales is available within the Welsh Dispensing Data Set (WDDS)[16], which is updated on a monthly basis. Within SAIL upon each monthly release of WDDS, a research ready data asset (RRDA) is created and maintained[17] based on COVID-19 population e-cohort RRDA[13], which enhances the dispensing data for research purposes with mapping to additional coding classifications and meta-data. Although primary care prescribing data is available for the population of Wales, it is not comprehensively mapped between Read and BNF. Therefore, in these analyses we have focused only on Welsh dispensing data.

Categorisation of CVD risk factor medications:
Medicines were selected from BNF Chapters 2 (Cardiovascular System) and 6 (Endocrine System)[18]. These were manually curated (initially by RS; reviewed by AS) selecting therapies used to treat and/ or licenced to treat CVD into 11 sub-groups: Antihypertensives, Antiplatelets secondary prevention (primary for DM), DOAC, Warfarin, Heparins, Lipid lowering, T2DM, Insulin, Heart failure, AF, Angina (**Supplementary Table 1)**.

Medicines were categorised according to their primary indication to prevent double counting. Hence most blood pressure lowering agents were classified as antihypertensives apart from some classes of beta blockers, loop diuretics (and some thiazides e.g. metolazone), and sacubitril/valsartan which are used specifically for heart failure. Like antihypertensives, other medicines may have more than one indication, e.g. SGLT-2 inhbitors are now additionally licenced for heart failure as well as T2DM, and anticoagulants used to treat AF (most commonly VKAs and DOACs) can also be used to treat deep vein thrombosis and pulmonary embolism. This may result in undercounting for medicines used for some CVDs in these analyses and in particular heart failure as a condition may be under-represented.

Additional analyses could be carried out linking to disease codes although this was out of scope for the analyses presesented here.

Insulin preparations and other glucose lowering therapies for T2DM were categorised separately, although it is well known that a proportion of individuals with T2DM will also be on insulin. However, understanding the trends over time in the separate categories may be important specifically in tracking incident T2DM. Anticoagulants were categorised on their own and by class: vitamin K antagonists (VKA), direct oral anticoagulants (DOAC) and heparins. This allowed analysis of behaviours within the anticoagulant category; for example, differential use of VKAs and DOACs during the pandemic. Antiplatelets were classified on their own as they can be used for primary and secondary prevention for MI, stroke and peripheral vascular disease (PVD). An additional and separate category of medicines that are mainly used as anti-anginals was created.

Excluded medicines were all intravenous preparations, those used to treat pulmonary hypertension, anti-arrhythmics where the indication is unlikely to be AF, sclerosants and medicines with very low prescription rates.

Medication Data Processing

A detailed description of the medications data processing undertaken in each national TRE is given at https://github.com/BHFDSC/CCU014_01. For all analyses (except the interrupted time series analysis – see below), dispensing data were used as these are more likely to be indicative of individuals taking medicines and were available in all three nations. Within the English TRE, the NHSBSA dispensing dataset was screened to identify all possible dispensed medicines. Both dispensing and prescribing data were mapped to the British National Formulary (BNF)[18] (via Dictionary of Medicines and devices (DM+D) or SNOMED concepts), and the medication substance identified using the 8th BNF character to facilitate categorisation according to CVD sub-group.

Analyses in the Scottish National Safe Haven & SAIL Databank used the same inclusion criteria, code lists and categorisation for CVD medicines, using BNF codes selected and extracted from the English TRE, with adjustments as required to accommodate specific features of the datasets in each. Summary output files from each nation were extracted and combined with results from other nations.

Details of Medications Data Processing by nation

England

NHSBSA data comprise prescriptions for medicines that are dispensed or supplied by community pharmacists, appliance contractors and dispensing doctors in England. The data also includes prescriptions submitted by prescribing doctors, for medicines personally administered in England. NHSBSA data were screened to produce a master list of all medications with any record of being dispensed[9]. Medicines are identifiable by a BNF or DM+D code. Medicines were selected on the basis of a unique combination of British National Formulary (BNF) and Dictionary of Medicines and Devices (DM+D) codes. This combination permitted identification of all unique medicines and facilitated mapping to CVD categorisation. 32,574 unique medicines with distinct BNF codes (each specific combination of substance-pack-concentration) were taken forward for analysis. CVD medicines were selected from these using the categorisation described.

Dates in NHSBSA reflect the month in which the script was submitted for payment rather than the date a medication was dispensed to the patient; whereas the date variable in the prescribing (GDPPR) data reflects the actual day on which a medication is prescribed by the GP. The first available month of NHSBSA data is April 2018; we therefore applied an April 2018 start date to the majority of analyses. The analysis end date was the latest available monthly download at time of analysis for NHSBSA and the most recent prescriptions available in the prescribing data at the time of analysis (31st May 2021).

Age was calculated at the date of dispensing for each medication by subtracting the month and year of birth from the dispense date. For stratified analyses, demographic and regional data were linked from other NHS Digital primary and secondary care data via the pseudo-identifier ID (a non-identifying unique master key that replaces the NHS number following linkage).

Scotland

The Scottish Prescribing Information System (PIS) provides a repository for all community prescribing related information, including payments, but excluding prescriptions dispensed in hospitals.[19] PIS comprises three different records/sources of data: 1) ePrescribed – details submitted through the prescribing system (usually a GP practice), 2) eDispensed – details submitted through the dispensing system (community pharmacy), 3) DCVP – details used for payment to the pharmacy. The dispensed data in this study contains those prescriptions which have been processed completely through the system from prescription to payment. Prescriptions may be missing from the available dataset if they have not been presented to a community pharmacy for dispensing, if the prescription was not paid for through the NHS (e.g. if it was a private prescription), or if the Community Health Index (CHI) number (the unique identifier of patients in Scotland) was missing for any reason and the record could not be linked to an individual. The dates in the individual records include the date the prescription was issued, the date it was dispensed, and the date payment was made. Dispensed dates are not necessarily real dates but could be default dates, for example the last day of a month. Data are available from April 2009, but the data requested for CVD-COVID-UK projects and available on the Safe Haven is from 1st January 2015 onwards.

Ethnicity is not available as part of the PIS data on the Scottish National Safe Haven. More generally ethnicity has historically not been reliably recorded in Scottish health care records, with the coding scheme used in the Scottish Morbidity Records changing to use Scottish Census 2011 Ethnicity Categories in 2011 (mandatory since 1st April 2012). A different coding scheme is in use by the National Records of Scotland. There have been recent improvements in data collection in response to the UK Government's Equality Act. This should allow a more accurate categorisation going forward.[20] Ethnicity data from Scotland are therefore not included in these analyses.

Wales

Dispensing data: The available range of Welsh Dispensing DataSet (WDDS) at the time of this study was from 1st January 2016 to 25th August 2021. The raw data arrives in two separate extracts, one including all dispensed items per practice (each person within a general practice setting is identified by a unique ID in the data extract) and the other including an anonymised linkage field (ALF) that enables linkage of dispensing records to other available patient information[16]. Within WDDS, all medications are coded in DM+D. We established a pipeline that is applied to each monthly release of WDDS data that links both ALF and Dispensing record tables and maps drug items from DM+D codes to BNF. NHSBSA was used to map all dispensed items from DM+D codes to BNF coding system[21]. Details of mapping strategy and syntax is provided at https://github.com/BHFDSC/CCU014_01. In order to match the existing data range available in England and Scotland, a snapshot of Wales data starting from March-2018 up to May-2021 was used for these analyses.

Age was calculated at the date of dispensing for each medication by subtracting the week of birth (Monday) from the dispense date.

Ethnicity data were extracted from a combination of electronic health record data sources, and harmonised into a composite national ethnicity spine which corresponds to the Office for National Statistics (ONS) breakdowns of ethnicity categories for the population of Wales, in the following five groupings: White, Asian, Black, Mixed and Other.

Study Population

Inclusion criteria:
These analyses focused on medicines data with linkage to individual data for demographic characteristics (**Figure 1**). We included medications dispensed to individuals who were aged between 18 and 112 years, with sex reported as male or female and at pharmacies in the relevant nation. We excluded individuals with a date of death recorded before 1st April 2018 or a null date of birth. Medications dispensed between 1st April 2018 and 31st July 2021 were included in all three nations. For stratified and incident analyses medication records were required to have a valid pseudo-identifier ID (a non-identifying unique master key that replaces the NHS number following linkage) to enable linkage to socio-demographic and regional characteristics. See **Figure 1** for a flowchart of the selection of data for analysis, linkage, and corresponding counts from data sources.

Sub-groups:
We analysed results within subgroups according to key demographic characteristics of interest, including: age (categorised >=18-29 and thereafter in 10 year age bands to 90+ years), sex, ethnicity (categorised as Black, White, Asian, Mixed, Other) and region (categorised as East Midlands, East of England, London, North East, North West, South East, South West, West Midlands, Yorkshire and The Humber, plus Scotland and Wales). Individuals with missing values for a given stratification variable are reported as a separate group for those sub-analyses.

Statistical Analyses

Trends in dispensed medications:
We counted items dispensed for the medicines of interest from 1st April 2018 to end July 2021. We also calculated monthly percentage change compared to the previous year in dispensed medications from April 2019 to July 2021. Analyses were conducted for the combined group of CVD medicines and separately for the major CVD sub-groups: antihypertensives, lipid-lowering medications, T2DM and insulin.

Stratification by sub-groups (CVD and socio-demographic)
Monthly counts and their percentage change were calculated for each of the 11 CVD sub-groups for both prevalent and incident medications. We also investigated variation in dispensing of prevalent medications by age, sex, region and ethnicity.

Interrupted time series analyses
Interrupted time series (ITS) using segmented regression, following Bernal et al.(2017)[22], was used to evaluate the impact of the COVID-19 pandemic and associated restrictions on prescription of CVD medicines in England. Weekly counts data were modelled from June 2018 to May 2021 comprising 153 data points, including data both prior to the first national lockdown and into 2021 after the third national lockdown. Preliminary inspection of data using scatterplots was undertaken to help identify the underlying trend and outliers. We defined a priori segments for anticipated regular effects associated with the two-week period including Christmas and New Year each year and the two-week period prior to each of these events. Outside these periods, prescription of CVD medicines is relatively consistent month to month and, unlike CVD events, not expected to be higher in Winter. We introduced segments corresponding to the four-week periods prior to national lockdowns (23rd March 2020, 5th November 2020) and one week prior to the final lockdown (6th January 2021; shortened due to overlap with the Christmas & New Year period 2020-21). Evidence of autocorrelation was assessed through examination of the residuals, autocorrelation plots and with Durbin's and Breusch Godfrey tests. To account for possible autocorrelation, ARIMA models were fitted to each CVD sub-group following Schaffer et al. (2021)[23]; these models also have the benefit of the moving average process and accounting for non-stationary state. This analysis was undertaken using the auto.arima function from the forecast package in R.

Incident CVD medications
To calculate person-level incident medication within each CVD sub-group we identified any new dispense or any dispense more than 365 days after a previous one in the same CVD sub-group. We allowed an initial clearance window for the first year of data availability to allow monthly incidence counts to stabilise. This was to correct for the high levels of artefact "incidence" in the first few months of the study period resulting from records first becoming available for analysis. Incident medications results are therefore presented from 1st March 2019 to 31st July 2021. Individuals may be counted as receiving incident medication for more than one of the CVD sub-groups. Linear, cubic and ARIMA regression models were fitted to the pre-lockdown period March 2019 to February 2020 and used to predict expected incident counts for the post-lockdown period April 2020 to July 2021. March 2020 was excluded from the pre-lockdown period to avoid inflating the expected counts. Differences in the number of incident medications by CVD sub-group in the post-lockdown period were calculated by subtracting the observed monthly count from the predicted monthly count. Results from the linear models are presented**.**

Impact of missed treatment on future CVD events
Whilst a full economic analysis was out of scope for this analysis, taking hypertension as an example, we estimated the potential impact of missed cardiovascular risk factor treatment on CVD events using the most recent cost-effectiveness analysis model developed for the National Institute of Health and Care Excellence (NICE) (NICE guideline NG136)[24], adapting the base case to reflect characteristics of the hypertensive population not receiving incident medication. We chose hypertension because it is the most common CVD risk factor for which medicines are prescribed. We identified characteristics of the 2019 population receiving incident antihypertensive medication (mean age and proportion male/female, with T2DM and smokers) within the English TRE. Using this information in the QRISK2 calculator[25] we calculated weighted 10-year QRISK2 scores for the NICE treatment effect model base case, additionally specifying SBP at 150mmHg (the threshold for stage 2 antihypertensive treatment using home blood pressure monitoring). Inputting these 10-year QRISK2 scores into the NICE model, we calculated the number of CVD events expected with and without hypertensive treatment (including stratification by stable and unstable angina, MI, transient ischaemic attack, stroke and heart failure). We scaled the number of CVD events per 1000 to the number of people with missed incident medicines for the treatment of hypertension observed in our analyses across England, Scotland and Wales.

Sensitivity analyses
To account for the potential impact of higher mortality due to the COVID-19 pandemic itself, in sensitivity analyses we exclude medications dispensed to individuals who died from COVID-19[26] and separately from any cause across the study period.

Public and Patient Involvement
The project was approved by the BHF DSC Approvals & Oversight Board which included patient and public partners, who were also consulted as data were produced and provided input into the final manuscript.

Results

We present results for the four CVD sub-groups representing the major CVD risk factor / disease groups of antihypertensives, lipid-lowering medications, T2DM and insulin). Additional tables and figures for the remaining seven CVD sub-groups are available in the **Supplementary Material** (AF, angina, DOACs, warfarins, heparins, antiplatelets and heart failure).

Trends in the dispensing of CVD medications:
Overall, we observed a downward trend in CVD medicines dispensed over the course of 2020 and into 2021 suggesting a decline in the active management of CVD in the population (**Figure 2**). There was

an increase in total items of medications dispensed for the combined CVD sub-groups of hypertension, dysliplidemia and diabetes (including insulin) in the immediate pre-pandemic period (+11.8% March 2020 versus March 2019) (**Figure 2; Supplementary Table 2**). This compared to annual monthly percentage change ranging between -1.4 and 4.9% in the year before pandemic onset. Year-on-year dispensing did not fall below 2019 levels until May 2020 when initial lockdown restrictions were beginning to be relaxed. Dispensed items again fell below 2019 levels in August 2020 (-9.3%), October 2020 (-1.2%) ahead of the second national lockdown and November 2020 (-0.3%). In comparison, year-on-year dispensing was 4.7% higher in December 2020 ahead of the third national lockdown. The number of medicines was below the previous year throughout early 2021 until April. Mean quantity per dispense remained stable over time within most CVD sub-groups, except for a brief increase in March 2020, followed by a smaller decline in April 2020 (**Supplementary Figure 1**). Exceptions to this include insulin and DOACs where mean quantity per dispense declined over the study period.

Trends by CVD sub-groups, proxied by prevalent medicines:
The general pattern of sharp growth in year-on-year medicines dispensed in the pre-pandemic period followed by dispensing below 2019 levels in May 2020 is seen across the CVD sub-groups (**Figure 2**). The most marked spike was observed for insulin at +24% in March 2020, followed by dispensing levels below 2019 in May and August 2020. Marked changes were also observed for dispensing of anticoagulant medicines with an acceleration in the decline in warfarin during 2020-21 after an initial spike in March 2020 (**Supplementary Figure 2)**. In contrast DOAC dispensing maintained year-on-year growth, but the rate of growth declined (**Supplementary Figure 2**).

Dispensing trends by socio-demographic characteristics are presented in **Supplementary Figures 3 & 4**). A valid pseudo-identifier ID is required for linkage with individual demographic characteristics; the proportion of data linked increased over time within the English dispensed data (**Supplementary Figure 5**) and this should be considered when interpreting socio-demograpahic trends. Data were missing on region for 6.5% of dispensed CVD medications and on ethnicity for 1.6%. The highest year-on-year uplifts ahead of the first national lockdown were observed in the age bands 18-29 and 30-39. Similar patterns were observed in males and females. Yorkshire and The Humber saw the most pronounced year-on-year uplift in dispensed medicines associated with the first national lockdown and further subsequent peaks in June-July and September reflecting additional local restrictions during those times. London also saw more marked uplifts for subsequent peaks compared to other regions, including in December, coinciding with the earlier local introduction of Tier 4 restrictions[27]. Similar trends were observed in Scotland and Wales with marked change in year-on-year dispensing associated with the first national lockdown. Black individuals had a delayed uplift in dispensing with year-on-year growth peaking in April 2020 rather than March. A more detailed breakdown by ethnic group is available for England (see **Supplementary Figure 3c**).

Interrupted time series analyses
We observed a sharp increase in the prescription of CVD medicines in England prior to the first national lockdown, similar to increases characteristically observed prior to Christmas (**Supplementary Figure 6a & 7a**). However, unlike Christmas there was no clear subsequent drop in medications prescribed in the week(s) immediately following. The period between the first and second national lockdowns was characterised by declining CVD prescriptions, and, unlike before the first lockdown, there was no clear uplift in CVD prescriptions observed in the four-week period preceding the second national lockdown (**Supplemenary Figure 6b & 7b**). There was some evidence that the third national lockdown was preceded by a week of uplift, although the overlap with Christmas and New Year fluctuations complicates interpretation. A similar pattern was observed across all CVD sub-groups. Terms selected by the auto ARIMA analyses are available in **Supplementary Table 3**; autoregressive terms were only returned for warfarins.

Trends for incident CVD medications:
We observed a marked decrease in incident dispensing for antihypertensives, lipid-lowering medications and T2DM medications in the immediate post-pandemic period (**Figure 3**). The easing of

lockdown restrictions in May 2020 was followed by a slow recovery in incident medications, but this recovery plateaued with the second and third national lockdowns (5th November 2020 and 6th January 2021 respectively). Incident medications continued to recover through the first half of 2021, with a spike in March 2021 coinciding with the end of the "stay at home" message; however, levels remained markedly lower than in the pre-pandemic period. On average 45,849 (95%CI 32,298 to 59,401) fewer patients per month were being commenced on antihypertensives and 41,456 (95%CI 31,106 to 51,805) fewer patients on lipid-lowering medications per month compared with predicted levels based on th pre-pandemic period (**Table 1**). The equivalent change for T2DM was 12,287 (95% CI 7,686 to 16,887) less incident patients per month.

Impact of missed treatment on future CVD events:
During the period April 2020 to end May 2021, 733,586 (95%CI 516,763 to 950,409) fewer individuals initiated antihypertensive treatment across England, Scotland and Wales than would have been expected had 2019 incident treatment levels sustained. Using the NICE hypertension treatment model[24] we estimated that 20,399 additional CVD events would result from the non-initiation of hypertension treatment associated with the COVID-19 pandemic, were these individuals to remain untreated for the duration of their lifetime (**Table 2**). This would equate to an additional 3,406 myocardial infarctions and 5,188 strokes resulting from the under-treatment of hypertension alone during the period April 2020 to July 2021. If, however, individuals could be identified for treatment within five years this would reduce the total number of CVD events associated with the pandemic to 4,055 CVD events; suggesting that at least 2,321 myocardial infarctions and 4,501 strokes can be avoided. We did not estimate CVD outcomes for other risk factors (e.g. lipid lowering, T2DM medications), or the additive risk of having one or more of the CVD risk factors. In addition, we considered first treatment with any antihypertensive (rather than specific medicines), including individuals commencing on more than one agent as well as those commenced on monotherapy. As such, we have generated conservative estimates of CVD events associated with non-treatment of CVD risk factors due to the pandemic.

Sensitivity analyses:
Excluding medications dispensed to individuals who died from COVID-19[26] and from any cause we observe trends consistent with those presented in our main findings (**Supplementary Figures 9 &10**), suggesting that the declines observed do not result from the excess mortality of these individuals.

Discussion:

The UK has comprehensive national medical records which can track health over the life course. We present the largest study to date using English, Scottish and Welsh data together to describe patterns in dispensed medications. Developing a novel method of categorising medicines for an indication, we have used the unique capability of linked records to describe how the use of medicines to manage CVD has changed during the course of the COVID-19 and the impact that this could have on future CVD health as a measure of the indirect impact of COVID-19. Whilst this work is limited to Great Britain, it is likely that this is reflective of similar health economies, and paints a sobering picture of CVD health in the coming years if it is not addressed. This work complements and meaningfully extends other evidence on the indirect health impacts of the pandemic.[2,17]

Our main findings demonstrated the number of individuals who are likely to have missed having a major cardiovascular risk factor treated during the course of the COVID-19 pandemic and using existing models to assess the impact of this on future CVD events. Our data also demonstrate that whilst there has been some recovery in dispensing of medications from the initial declines following the first lockdown, crucial first detection of CVD risk factors as indicated by medicines has not returned to pre-pandemic levels. The numbers presented here are focused only on hypertension; a fuller analysis of the impact would need to include all CVD categories. Moreover using these data could be further supported by other measures such as blood pressure, lipids and glucose, although with reduced primary care visits during the pandemic, many measurements are likely to be missing[2-4]. Therefore this medicines method presents an important objective adjunct to existing research methods. In the UK ZOE COVID study, 34% of participants gained a mean of 3.7kg[28] and other adverse lifestyle factors have also been reported to have worsened (snacking, alcohol consumption, reduced physical activity), which will further contribute to the risk of hypertension, dyslipidaemia and T2DM[29]. Evidence from other countries also suggests that CVD risk factors may have increased during the course of the pandemic, including blood pressure[30].

Alternative explanations for the trends in CVD medicines observed include changing population dynamics of the UK and/or concurrent changes in the quantity of medications dispensed. However, the Office for National Statistics (ONS) data on mid-year population for 2020 which includes the period of disruption associated with the first national lockdown suggested that population growth remained at ~0.4%, a level consistent with the previous year[31]. Migration patterns also remained relatively constant, excluding this as a possible explanation. Deaths were ~67k higher than the five year average likely reflecting the impact of the COVID-19 pandemic; however in sensitivity analyses where we exclude medications dispensed to individuals who died from COVID-19[26] and from all-causes, we observed trends consistent with those presented in our main findings. For these reasons, changes in the demographic structure of the UK population are unable to explain the change in trends of CVD medicines observed during the study period. Another potential explanation would be changes in the quantity of medicines dispensed per item concurrent and in the opposite direction to changes in the volume of items. However, our analyses suggest that quantity of medicines per dispense remained relatively constant over the analysis period and that the small fluctuations observed would tend to inflate the count trends observed; therefore suggesting our medicines-based estimates of the impact of the COVID-19 pandemic are conservative. It is also possible that the hospitalisation of individuals with COVID-19 may have contributed to reduced medicines dispensed in the community although in preliminary analysis of hospital data (results not shown), we observed similar patterns for CVD medicines to those presented here for community dispense.

A major factor for reduced identification of CVD risk factors as well as what will determine recovery are the mechnisms for screening of CVD and its risk factors in primary care. Across GB, CVD risk factors are detected in primary care using mechanisms such as the Quality of Outcomes Framework (QOF) in England[32], the Quality Assurance and Improvement Framework (QAIF) in Wales[33] and the Transitional Quality Arrangements (TQA) Framework in Scotland[34]. During the pandemic primary care visits fell markedly, with many existing visits being replaced by electronic or telephone

consultations[2,3,5,35]. This mirrors a decrease in acute CVD events presenting to secondary care[36]. While there has been a re-opening of services during the pandemic, standard mechanisms of screening risk factors have not been wholly re-introduced[37]. Declines in consultation rates varied by age, ethnicity and region[3]; with some sub-groups known to have a higher risk of CVD and risk factors associated with CVD[38], including men, less affluent patients and immigrants, less likely to access remote consultations[39]..

Whilst it is likely that as services return to normal, cardiovascular risk in missed individuals may well be detected, it remains unclear what mechanisms are in place to re-introduce methods of screening or what consequences a delay in diagnosis might have. An important public policy consideration from these analyses is implications more generally about health service provision during pandemics and planning for how routine health care could be sustained despite demands on the overall system in the event of future pandemics. These analyses may provide mechanisms to identify and then target those at highest CVD risk. However, we must also identify alternative mechanisms of risk factor management incorporating support services in primary care e.g. primary care pharmacists and local pharmacies which may be able to address large numbers of less complex cases. Of course, differing health systems will have their unique structures and challenges but the patterns in dispense of CVD medicines we describe are likely to be similar in many high income (and potentially other) countries.

There are many further opportunities for uses of medicines data that are beyond the scope of the analyses presented here. It is now possible to link anonymised dispensing data with primary and secondary care data at individual level, facilitating detailed analysis of characteristics associated with life-course use and accumulation of medications (polypharmacy), adverse drug reactions and adherence. Understanding how medicines are being used can act as an objective barometer for the 'health' or disruption to a clinical pathway and, as these analyses demonstrate, may also help target recovery.

There are however a number of limitations worthy of discussion. Whilst we have used a medicines lens and applied a new categorisation of CVD medicines according to prescribed medicine use a limitation relates to the difficulty in assigning diseases for overlapping indications for some medications which may result in underestimates of certain CVDs. For example, heart failure is likely to be underestimated as management options overlap with hypertension and type-2 diabetes (e.g. ACE-I, beta blockers and SGLT-2 inhibitors). Our analysis could be extended in future work by linking to disease diagnosis codes to refine estimates for conditions such as heart failure. However, the analyses presented here do give an indication of the overall missed CVD risk factors to alert policymakers to the indirect impacts of COVID-19. The medication data analysed here represent "real world data" that were not collected for research purposes; it is possible that artefacts may exist within the data due to differences in collection, processing or transfer and these may vary over time and by source. For example, we observed a decline in the proportion of medications dispensed with invalid ("null") IDs over time in the English data, corresponding with an ongoing switch from paper-based to electronic processing[40]; this is relevant because valid IDs are required for linkage with other data to derive individual characteristics such as age, sex, ethnicity and co-morbidities.

The estimates derived on the impact of a reduction in medicines on CVD events rely on many assumptions that may change over time and in direct response to the pandemic. The final impact of the pandemic on CVD events in the UK is highly dynamic and will be responsive to many factors not captured by the model we use. These include future changes in population structure, underlying levels of CVD risk factors and their treatment (including non-pharmacological approaches), the additional impact of COVID-19 infection on future CVD risk, the rate at which "missed" individuals are identified for treatment and if the way CVD risk factors are actioned through medicines remains constant, i.e. guidelines remain constant. For these reasons, in this analysis, we do not attempt to make a comprehensive estimate of the impact of all missed CVD medicines treatment on all future CVD events but rather to illustrate, using hypertension as an example, the potential impact using an established, externally validated model. The aim is to highlight the public health importance of urgently identifying individuals for treatment and the clear potential for harm should they not be. A full cost-effectiveness

model required to fully expand on the impact of medicines estimates that are reported in these analyses for future CVD events was out of scope here, but would need take into account a revised base case with additional risk that COVID-19 itself may have on CVD risk (at least in the short term) and triangulate this with other CVD risk factors as well as timescales and economic impacts. However, the analysis does provide an indication of the scale of the potential issue which if not addressed could lead to substantial undertreatment in causal CV risk factors, thereby meaningfully worsening the impact of the pandemic.

These analyses demonstrate that medicines used as a proxy for disease can complement investigation using electronic health records and disease diagnostic codes. Such analyses can be incorporated into methods to identify and treat individuals who have missed treatment, and these are urgently required to avoid additional future CVD events. Whilst excess event predictions are by nature dynamic and reflect many, including some as yet unknown factors, we present such estimates to highlight the level of harm that could be done should systems not improve to promptly tackle and treat missed CVD risk factors. This medicines approach can provide policy makers with an additional lens to monitor healthcare pathways providing a rapid reponse tool in the event of a future pandemic or other similar disruption.

FIGURE 1: Flowchart showing selection of analytical datasets from NHSBSA (England)

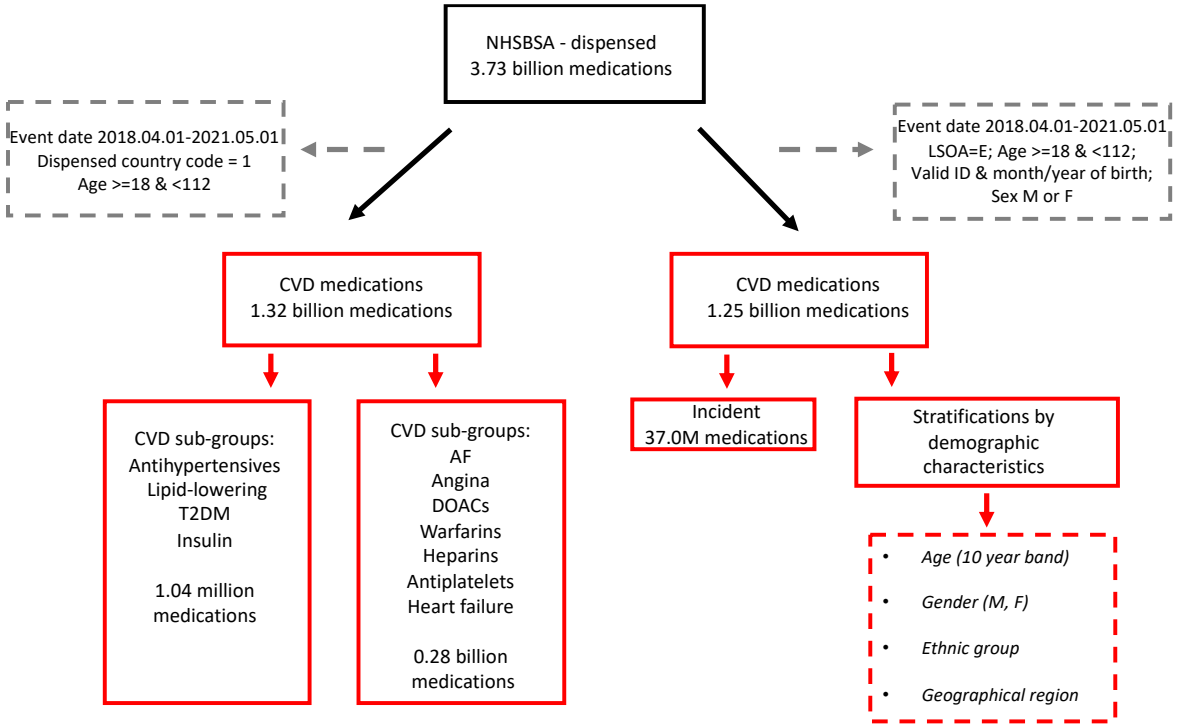
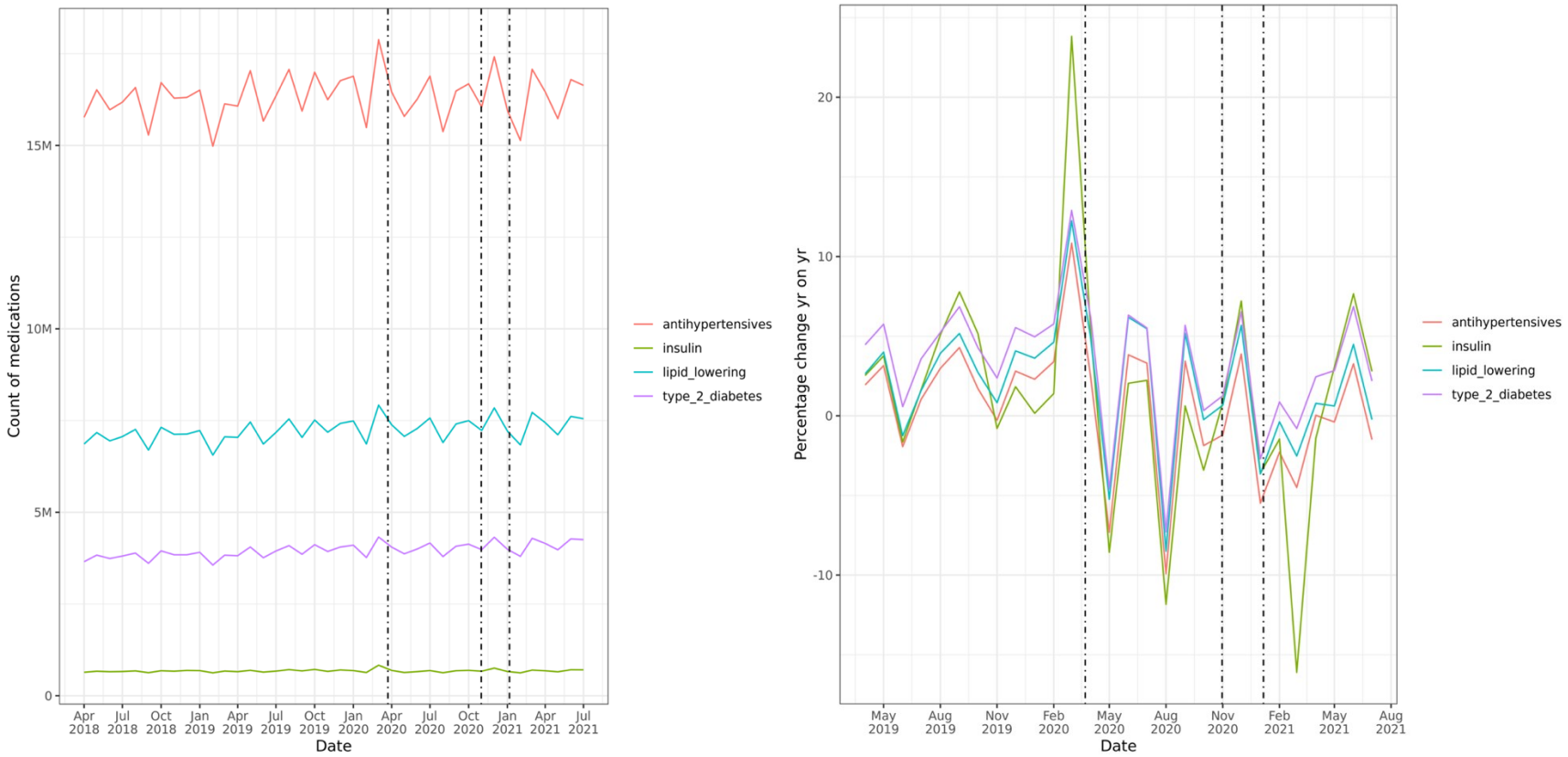
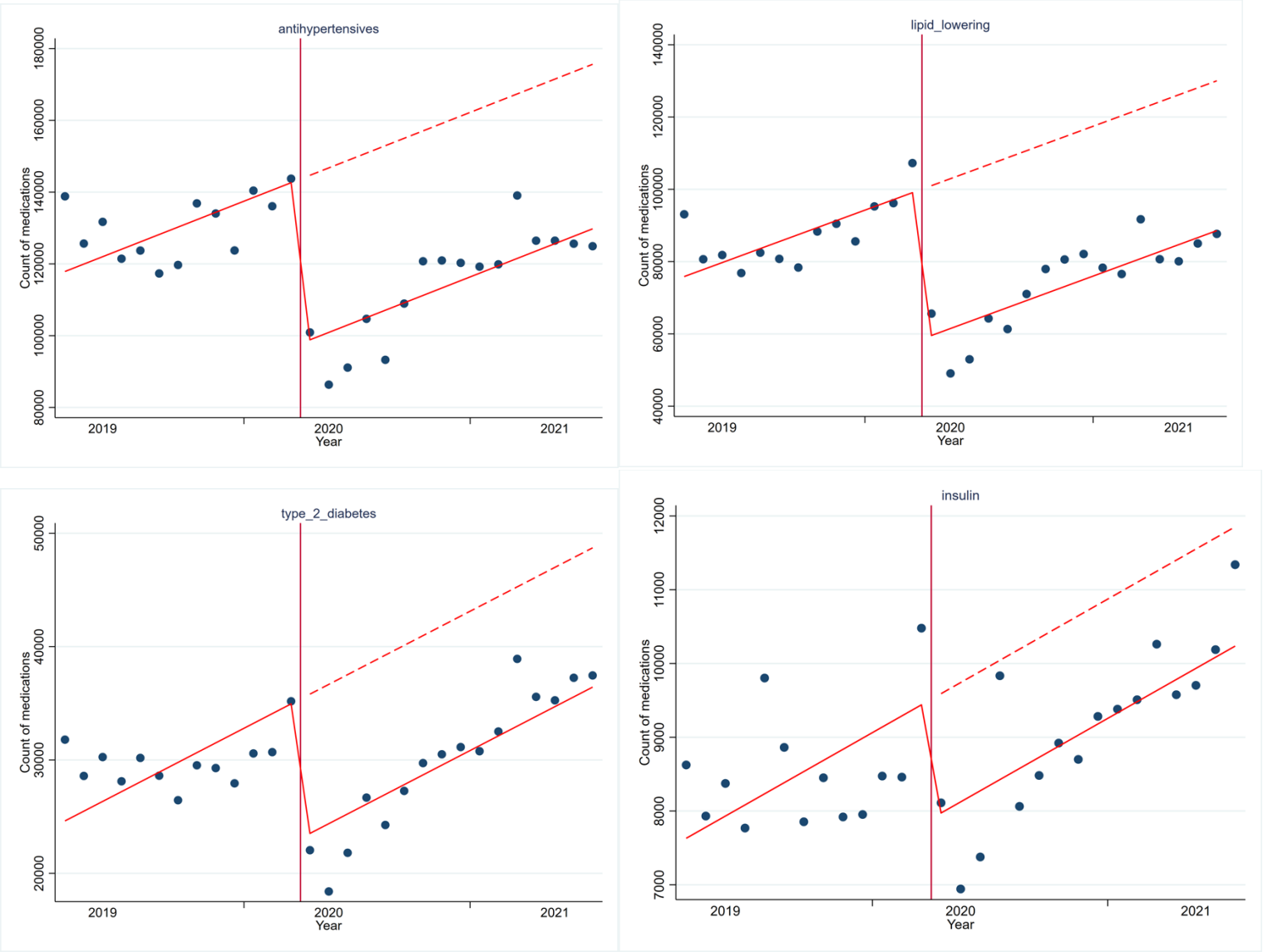


FIGURE 2: Trends in annual monthly counts and percentage change of dispensed CVD medicines for England, Scotland and Wales combined over course of pandemic by CVD/ CVD risk factor sub-groups



Footnotes: Dotted lines indicate timing of first, second and third national lockdowns: 26th March 2020, 5th November 2020 and 6th January 2021 respectively

FIGURE 3: Trend in count of incident medications dispensed by CVD/ CVD risk factor sub-group in England, Scotland and Wales, by month.



Footnotes: Vertical red line indicates timing of first national lockdowns: 26th March 2020.

The adverse impact of COVID-19 pandemic on cardiovascular disease prevention and management in England, Scotland and Wales: A population-scale analysis of trends in medication data

TABLE 1: Difference in incident medications dispensed by month (2020/2021 versus counterfactual predicted from linear model March 2019-February 2020) in England, Scotland and Wales by CVD/ CVD risk factor sub-group.

	Estimated difference from counterfactual					
	Monthly			April 2020 to July 2021 inclusive		
CVD sub-group	Estimate	LCI	UCI	Estimate	LCI	UCI
Antihypertensives	-45,849	-59,401	-32,298	-733,586	-950,409	-516,763
Lipid lowering	-41,456	-51,805	-31,106	-663,292	-828,885	-497,699
Type-2 diabetes	-12,287	-16,887	-7,686	-196,584	-270,197	-122,971
Insulin	-1,618	-2,768	-468	-25,881	-44,282	-7,480

TABLE 2: Estimated N CVD events resulting from missed antihypertensive initiation since March 2020 including data from England, Scotland and Wales; A) assuming non-treatment ongoing over lifetime, and B) non-treatment duration of five years

	QRISK2%	Treatment effect	Estimated N CVD events in "missed" treatment initiation population						
			Stable Angina	Unstable Angina	MI	Transient Ischaemic Attack	Stroke	Heart Failure	Total CVD events
A) Lifetime									
Male	11.3	NT	32,278	10,652	23,886	9,361	33,246	24,854	134,276
		Tx	29,050	9,683	21,626	8,715	31,632	24,208	124,915
		Additional cases pandemic (NT-Tx)	**3,228**	**968**	**2,259**	**646**	**1,614**	**646**	**9,361**
Female	4.9	NT	22,594	5,751	9,859	10,270	38,616	18,897	105,989
		Tx	19,548	4,920	8,713	8,981	35,042	17,744	94,950
		Additional cases pandemic (NT-Tx)	**3,046**	**831**	**1,146**	**1,289**	**3,574**	**1,153**	**11,039**
Total			**6,274**	**1,799**	**3,406**	**1,934**	**5,188**	**1,799**	**20,399**
B) 5 years									
Male	11.3	NT	5,164	1,937	5,164	968	2,259	1,291	16,784
		Tx	4,519	1,614	4,196	968	1,937	968	14,202
		Additional cases pandemic (NT-Tx)	**646**	**323**	**968**	**0**	**323**	**323**	**2,582**
Female	4.9	NT	2,987	1,075	735	1,471	2,105	576	8,948
		Tx	2,513	905	619	1,216	1,741	481	7,475
		Additional cases pandemic (NT-Tx)	**474**	**171**	**117**	**254**	**364**	**94**	**1,473**
Total			**1,119**	**493**	**1,085**	**254**	**687**	**417**	**4,055**

Footnotes: Estimates of number of future CVD events in individuals who missed initiation of antihypertensive treatment are derived from a Markov cohort model; further details on the model including its structure and parameter inputs provided in NICE Guideline NG136. Here, the cohort entering the model is considered to have SBP equal to 150mmHg (stage 2 hypertension home blood pressure monitoring SBP threshold). Each year the cohort may remain in the CVD free state or transition to a CVD state or death. The risk of having a non-fatal CVD event is determined by the QRISK2 score with the distribution across types of CVD events taken from Ward 2005. Hypertensive treatment is assumed to act directly on CVD risk with treatment effects taken from Brunström 2018. The model was run deterministically. Estimates of additional CVD events due to pandemic reflect: A) the number of additional CVD events that would be experienced by the cohort over the life-course were non-treatment to persist, and B) the number of CVD events if antihypertensive treatment were to be initiated after five years. Input parameters are based on the characteristics of the population who initiated hypertension treatment in England in 2019. This population was found to be 56% female with the mean age of females equal to 52 years, 4.8% of whom had a record of T2DM and 29.8% smoking; for males the mean age was 55 years, 6.4% with a record of T2DM and 28.0% smoking. The QRISK2 calculator was used to provide a 10-year QRISK2 score based on these characteristics weighted for prevalence of T2DM and smoking equal to 11.3% (male) and 4.9% (female) assuming SBP=150mmHg. The difference in N of

events per 1000 expected for treatment (Tx) and non-treatment (NT) based on these characteristics was scaled to the 733,586 individuals estimated to have missed treatment in England April 2020 - July 2021

Ethical approval
The North East-Newcastle and North Tyneside 2 research ethics committee provided ethical approval for the CVD-COVID-UK research programme (REC No 20/NE/0161).

Software and code availability and data sharing
All data preparation and analyses were conducted using Databricks (SQL, Python), R or Stata within the English TRE. All data preparation and analyses within the Scottish National Safe Haven were conducted on the secure analytical platform using R. All data processing in the SAIL Databank was performed using R. All code is available on GitHub https://github.com/BHFDSC/CCU014_01.

Data used in this study are available in NHS Digital's Trusted Research Environment (TRE) for England, but as restrictions apply they are not publicly available (https://digital.nhs.uk/coronavirus/coronavirus-data-services-updates/trusted-research-environment-service-for-england). The CVD-COVID-UK/COVID-IMPACT programme led by the BHF Data Science Centre (https://www.hdruk.ac.uk/helping-with-health-data/bhf-data-science-centre/) in partnership with HDR UK received approval to access data in NHS Digital's TRE for England from the Independent Group Advising on the Release of Data (IGARD) (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data) via an application made in the Data Access Request Service (DARS) Online system (ref. DARS-NIC-381078-Y9C5K) (https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services). The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board (https://www.hdruk.ac.uk/projects/cvd-covid-uk-project/)) subsequently granted approval to this project to access the data within the TRE for England, the Scottish National Safe Haven and the Secure Anonymised Information Linkage (SAIL) Databank. The de-identified data used in this study were made available to accredited researchers only.

Data used in this study are available in the Scottish National Safe Haven (Project Number: 2021-0102), but as restrictions apply they are not publicly available. Access to data may be granted on application to the Public Benefit and Privacy Panel for Health and Social Care (PBPP (https://www.informationgovernance.scot.nhs.uk/pbpphsc/)). Applications are co-ordinated by eDRIS (electronic Data Research and Innovation Service (https://www.isdscotland.org/Products-and-services/Edris/)). The anonymised data used in this study was made available to accredited researchers only through the Public Health Scotland (PHS) eDRIS User Agreement (https://www.isdscotland.org/Products-and-services/Edris/_docs/eDRIS-User-Agreement-v16.pdf).

Data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but as restrictions apply they are not publicly available. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy protecting data safe haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at https://www.saildatabank.com/application-process.

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The adverse impact of COVID-19 pandemic on cardiovascular disease prevention and management in England, Scotland and Wales: A population-scale analysis of trends in medication data

The study makes use of anonymised data held in the Scottish National Safe Haven. The authors would like to acknowledge the support of the eDRIS Team (Public Health Scotland) for their involvement in obtaining approvals, provisioning and linking data and the use of the secure analytical platform within the National Safe Haven.

This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make anonymised data available for research. We wish to acknowledge the collaborative partnership that enabled acquisition and access to the de-identified data, which led to this output. The collaboration was led by the Swansea University HDR UK team under the direction of the Welsh Government Technical Advisory Cell (TAC) and includes the following groups and organisations: the SAIL Databank, Administrative Data Research (ADR) Wales, Digital Health and Care Wales (DHCW), Public Health Wales, NHS Shared Services Partnership (NWSSP) and the Welsh Ambulance Service Trust (WAST). All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (IGRP) project number 0911.

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