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ORIGINAL RESEARCH

A Longitudinal Clinical Trajectory Analysis Examining the Accumulation of Co-morbidity in People with Type 2 Diabetes (T2D) Compared with Non-T2D Individuals

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ABSTRACT

Background: Type 2 diabetes mellitus (T2D) is commonly associated with an increasing complexity of multimorbidity. While some progress has been made in identifying genetic and non-genetic risk factors for T2D, understanding the longitudinal clinical history of individuals before/after T2D diagnosis may provide additional insights.

Methods: In this study, we utilised longitudinal data from the DARE (Diabetes Alliance for Research in England) study to examine the trajectory of clinical conditions in individuals with and without T2D. Data from 1932 individuals (T2D $n = 1196$ vs. matched non-T2D controls $n = 736$) were extracted and subjected to trajectory analysis over a period of up to 50 years (25 years pre-diagnosis/25 years post-diagnosis). We also analysed the cumulative proportion of people with diagnosed coronary artery disease

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(CAD) in their general practice (GP) record with an analysis of lower respiratory tract infection (RTI) as a comparator group.
Results: The mean age of diagnosis of T2D was 52.6 (95% confidence interval 52.0–53.4) years. In the years leading up to T2D diagnosis, individuals who eventually received a T2D diagnosis consistently exhibited a considerable increase in several clinical phenotypes. Additionally, immediately prior to T2D diagnosis, a significantly greater prevalence of hypertension (35%)/RTI (34%)/heart conditions (17%)/eye, nose, throat infection (19%) and asthma (12%) were observed. The corresponding trajectory of each of these conditions was much less dramatic in the matched controls. Post-T2D diagnosis, proportions of T2D individuals exhibiting hypertension/chronic kidney disease/retinopathy/infections climbed rapidly before plateauing. At the last follow-up by quintile of disadvantage, the proportion (%) of people with diagnosed CAD was 6.4% for quintile 1 (least disadvantaged) and 11% for quintile 5 ($F = 3.4$, $p = 0.01$ for the difference between quintiles).
Conclusion: These findings provide novel insights into the onset/natural progression of T2D, suggesting an early phase of inflammation-related disease activity before any clinical diagnosis of T2D is made. Measures that reduce social inequality have the potential in the longer term to reduce the social gradient in health outcomes reported here.

Keywords: DARE cohort; Longitudinal; Multimorbidity; Type 2 Diabetes

Key Summary Points

Why carry out this study?

There is a strong correlation between type 2 diabetes (T2D) and rising multimorbidity and treatment complexity. Identifying both genetic and non-genetic risk factors for T2D has made some progress. Individuals' longitudinal clinical histories before and after T2D diagnosis are expected to offer new information on the aetiology of diabetes and its complicated clinical course of multimorbidity.

What was learned from the study?

Several clinical characteristics were seen to steadily increase in the years before T2D diagnosis in those who subsequently received a diagnosis of the disease. The diagnosed hypertension (higher than in the control group) and asthma were the two most notable phenotypes among those that had been reported. The matched control group's trajectory over time was substantially less dramatic. Also, a larger signal of ischaemic heart disease proportion was seen just before T2D diagnosis.

These data imply a possible early stage of co-morbidity and disease activity before any clinical diagnosis of T2D is established.

INTRODUCTION

Type 2 diabetes (T2D) is a long-term condition characterised by persistently high levels of blood glucose due to either the inability to produce sufficient levels of insulin or body tissues becoming resistant to the action of insulin and, in many cases, a combination of the two factors [1, 2]. At least eight aetiopathogenic features of T2D are currently recognised [3].

T2D is often associated with other conditions, particularly disorders affecting the vascular system, although greater emphasis is usually placed on the diagnosis of T2D and on the progression of the disease following its diagnosis [4].

Clinical variability in T2D is acknowledged to occur [5, 6]. The aetiology of T2D is still unknown, although it is evident that both genetic and non-genetic risk factors interact and add to the likelihood of acquiring this disorder [7–10]. T2D is clearly linked to chronic overweight and obesity and a sedentary lifestyle. Numerous additional comorbid illnesses are frequently discovered at the same time at T2D is diagnosed, or they develop later [11, 12]. Low-grade inflammation is a key feature of T2D and has been reported to precede its development [13] while also being observed even in individuals before the development of T2D [14].

The intricate associations between multimorbidity's causal link and risk hierarchy in the context of T2D are mostly unknown. Cross-sectional and case–control epidemiological studies have been used to identify the majority of T2D-related illnesses, with environmental variables also being implicated [11, 12]. While these studies have been a valuable beginning point, longitudinal studies are the preferable method since they offer a better overall perspective.

Building on previous work in this area, but with a much larger cohort, the main goals of this longitudinal study were to identify any temporal continuums of comorbidity or clinical signs which predate the onset of diabetes and to map the documentation of significant health issues in people with T2D compared to those without T2D over a time continuum spanning from up to 25 years before and 25 years after a clinical diagnosis of T2D.

With this study, we have built on the findings of our previous paper [15], with a much larger cohort taken from across the conurbation of Greater Manchester, while also examining the relation between sociodemographic situation and longitudinal health outcomes in relation to cardiac conditions and lower respiratory tract infections.

METHODS

In this study, we utilised longitudinal data from the DARE (Diabetes Alliance for Research in England) [16] study (Greater Manchester subcohort) to examine the trajectory of clinical conditions in individuals with and without T2D. Data from 1932 individuals (T2D $n = 1196$ vs. matched non-T2D controls $n = 736$) were extracted and subjected to trajectory analysis over a period of up to 50 years (25 years pre-diagnosis and 25 years post-diagnosis). The DARE study recruited people with diabetes from specialist clinics and general practices in Greater Manchester from 2007 until 2017. The participants gave permission for their health records to be accessed in relation to coded diagnoses according to the READ code system historically (https://www.scimp.scot.nhs.uk/better-information/clinical-coding/scimp-guide-to-read-codes: accessed 20 July 2023) and more recently the SNOMED classification (SNOMED CT—NHS Digital: accessed 20 July 2023). The permission given at recruitment to the DARE study relates to any coded data, including diagnoses, health problems, metabolic variables and anthropometric measures together with demographic characteristics.

A similar methodology has been presented in an earlier study [15], but with a different data source and a much smaller number of patient records examined. The control participants in the present study were all recruited at the same time as the T2D cases, albeit there were fewer non-T2D controls. Occasionally several of the T2D individuals had the same age of diagnosis, enabling one control to be matched to more than one T2D individual.

Conditions were combined for further analysis. Specifically, we plotted the trajectories of chronic obstructive pulmonary disease, asthma, major mental disorders, hypertension, stroke, chronic kidney disease (CKD), respiratory tract infection, retinopathy, heart conditions (heart failure, myocardial infarction, angina, coronary angioplasty, coronary artery bypass graft [CABG] and coronary heart disease [CHD]) and eye, nose and throat infections (pharyngitis, sinusitis and conjunctivitis). Other diagnoses

included were: depression, psychosis, liver disorder, gastrointestinal disorder, inflammatory bowel disorder and connective tissue disorder.

The DARE study [16] recruited people with diabetes and non-diabetes controls from across several sites in England for longitudinal follow-up and biomarker analysis. The study is a collaboration between patients and professionals to provide a research resource to enable further study into the causes and complications of diabetes in its various forms. This study has established an epidemiological-based cohort of patients with diabetes across England.

The Greater Manchester Care Record (GMCR) [17] pools information from all general practices across the conurbation, with a total population base of 2.85 million people, and includes all currently collected primary care data. It provides a comprehensive database covering 99% of general practices in the conurbation.

Time Frame and Creation of Longitudinal Plots

A period of 25 years before the diagnosis of T2D (or the corresponding age in non-T2D persons) and up to 25 years beyond this time point were included in the study period. All coded diagnoses and demographic descriptions were among the data fields sought. We examined how diagnoses accumulated over time and their relationship to each person's date of T2D diagnosis or similar age for the controls. We counted the number of people (nc) who were developing the related morbidity in a particular year, as well as the number of people (nd) in the T2D cohort, in order to determine the trajectory of different clinical events in connection to the moment of diagnosis of T2D.

To describe the changes in the "tendency" of relevant morbidity across years, we identified both before and after the moment of clinically identified T2D; that is, pre- and post-diagnosis with T2D, we computed the ratio (nc/nd) and plotted it against time (year). In order to create the morbidity prevalence curves, we also conducted a similar study in non-T2D age- and gender-matched participants recruited to the DARE project, using the age at T2D diagnosis in their T2D counterparts (matched pair) as the comparable age for comparison.

Demographic Stratification

We also analysed the cumulative proportion of people with diagnosed CHD in their general practice (GP) record (defined as coded angina, myocardial infarction, heart failure, CABG or coronary angioplasty) mapped by quintile of social disadvantage (Townsend index score) [18] over a 25-year period prior to the age of diagnosis with T2D and for up to 25 years after diagnosis, with a parallel analysis for diagnosis of lower respiratory tract infection (RTI) as a comparator group. The social disadvantage quintiles were compared using analysis of variance (ANOVA).

Compliance with Ethics Guidelines

All participants gave explicit permission for their prospective health records to be accessed. Ethical permission for access to the prospective health records for DARE study participants is extant until 2043 [16]. Data access for the project was approved and overseen by Health Innovation Manchester [17] (reference number RQ019; data approval 02 June 2022). The study was performed in accordance with the Declaration of Helsinki and was approved by Health Innovation Manchester.

RESULTS

The mean age of diagnosis of T2D was 52.6 (95% confidence interval [CI] 52.0–53.4) years (Table 1). As a group, those individuals with T2D had a higher level of social disadvantage than the matched controls. Of the T2D individuals, 43% were female and 14% were of non-white ethnicity.

Our analysis revealed that in the years leading up to T2D diagnosis, individuals who eventually received a T2D diagnosis consistently exhibited a considerable increase in several clinical phenotypes. Additionally, immediately prior to T2D diagnosis, a

Table 1 Characteristics of the cohorts with type 2 diabetes and the controls

Characteristics	Control cohort		T2D cohort	
	Mean	SD	Mean	SD
Age (years)	66.1	16.11	67.7	12.3
Gender proportion (female, %)	46		43	
Age of diagnosis (years)	50.6	22.7	52.6	13.9
Median Townsend index score	0.2	3.6	0.7	3.7
Median Townsend quintile	3	1.5	4	1.5
Number of individuals	736		1196	
Ethnicity (white proportion, %)[a]	81		86	

SD Standard deviation, *T2D* type 2 diabetes
[a]Unknowns were excluded

significantly greater prevalence of hypertension (35%), RTI (34%), heart conditions (17%), eye, nose and throat infections (19%) and asthma (12%) was observed. The corresponding trajectory of each of these conditions was much less dramatic in the matched individuals of the control group. Post-T2D diagnosis, the proportions of T2D individuals exhibiting hypertension, CKD, retinopathy and infections climbed rapidly before plateauing; additionally, heart conditions and asthma continued to increase in this group (Fig. 1). The period for which we had coded data varied from 10.5 years to 75.9 years, which also takes into account the transfer of data from historical GP paper records (called the 'Lloyd George patient records') to digital records.

At the last follow-up, analysis by the Townsend index quintiles of disadvantage revealed that the proportion (%) of people with diagnosed CHD (denoted as 'heart condition' in Fig. 2) was 6.4% for quintile 1 (least disadvantaged), 4.0% for quintile 2, 6.1% for quintile 3, 9.8% for quintile 4 and 11.0% for quintile 5 (F = 3.4, p = 0.01 for difference between quintiles). For RTI, the corresponding percentages diagnosed with RTI were 12.0% for quintile 1, 8.7% for quintile 2, 13.1% for quintile 3, 17.0% for quintile 4 and 21.7% for quintile 5 (F = 4.2, p = 0.008 for difference between the quintiles).

DISCUSSION

The findings of our study provide novel insights into the onset and natural progression of T2D, suggesting an earlier pro-phase of inflammation-related disease activity before any clinical diagnosis of T2D is made. Further studies on a larger cohort of patients are suggested to explore the possibility of establishing associated predictive risk scores. In addition, we have built on previous findings [19] to describe how social disadvantage is associated with more adverse cardiac outcomes over time in people with T2D, with a similar pattern seen for RTIs. The determinants of health outcomes are complex. Measures that reduce social inequality have the potential—in the longer term—to reduce the social gradient in health outcomes described here [20].

The "end product" of more complicated underlying early alterations in homeostatic or early pathogenic pathways is frequently clinical. Longitudinal studies are essential for evaluating and identifying pre-diagnosis indications and the early alterations that may be corrected by behavioural or therapeutic therapies. These studies allow for the recording of such clinical signs and biomarkers well before a T2D diagnosis is ultimately made. Importantly, in relation to the way that the findings were derived in the present study from the available data, most people diagnosed with T2D in England are managed in primary care settings, from which our data were derived.

Large cohort population studies provide such insights [21, 22]. As an alternative, several countries and limited geographic regions have created primary and secondary electronic health data records, which are increasingly supplying important longitudinal resources for carrying out epidemiological investigations. In order to address such levels of multifactorial complexity, artificial intelligence and machine learning analytics are now offering a powerful set of tools [23].

The main goal of this study was to detect any temporal continuums of comorbidity or clinical indications which predate the onset of diabetes

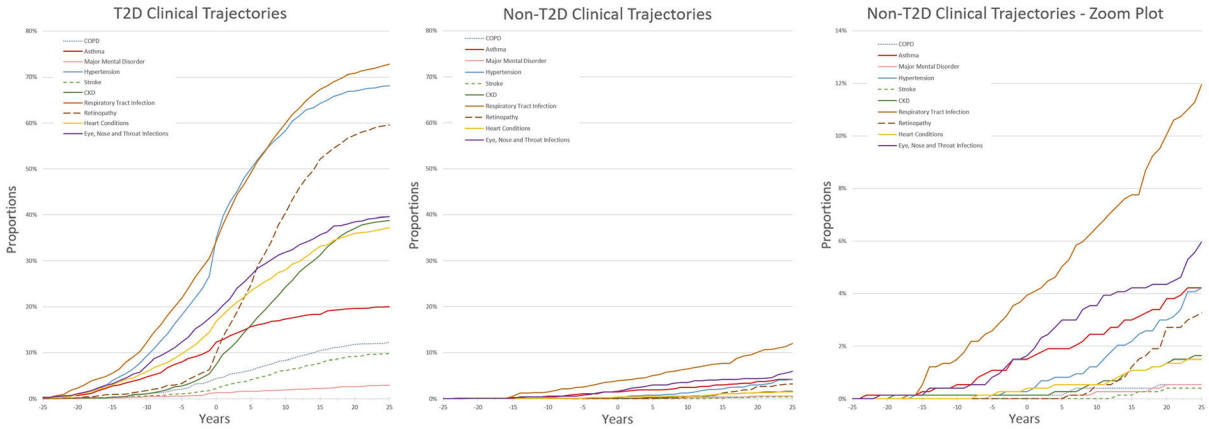

Fig. 1 Clinical trajectories for up to 25 years before (− 25 years) and 25 years after (+ 25 years) the diagnosis of T2D or an equivalent age for non-T2D individuals are shown as a proportion of the total number of people. T2D: For each plot, the numbers of people at each year point are: − 25 years, n = 901; − 20 years, n = 985; − 15 years, n = 1023; − 10 years, n = 1100; − 5 years, n = 1145, 0 years, n = 1196; + 5 years, n = 1034; + 10 years, n = 988; + 15 years, n = 645; + 20 years, n = 591; + 25 years, n = 499. Non-T2D: For each plot, the numbers of people at each year point are: − 25 years, n = 461; − 20 years, n = 501; − 15 years, n = 578; − 10 years, n =645; − 5 years, n = 698, 0 years, n = 736; + 5 years, n = 667; + 10 years, n = 588; + 15 years, n = 501; + 20 years, n = 417; + 25 years, n = 381. *CKD* Chronic kidney disease, *COPD* chronic obstructive pulmonary disease

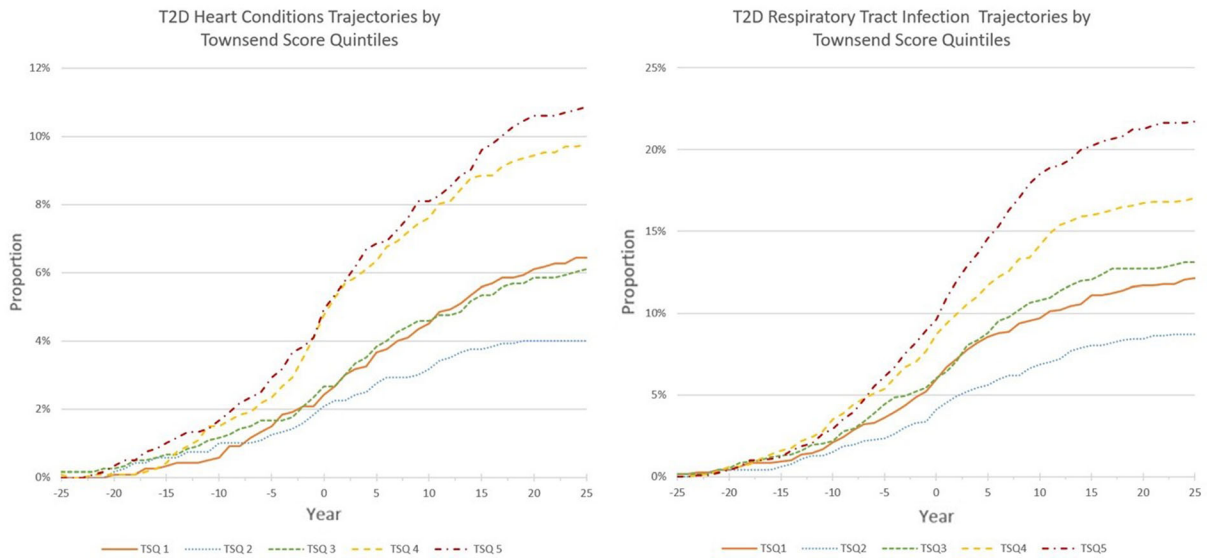

Fig. 2 Heart condition trajectory and respiratory tract condition trajectory for T2D individuals from 25 years before diagnosis to 25 years after diagnosis by Townsend index score quintiles (*TSQ*)

and to document the important health difficulties in persons on a time continuum spanning from before and after a clinical diagnosis of T2D. Longitudinal clinical histories before and after T2D diagnosis are expected to offer new information on the aetiology of diabetes and its complicated clinical course of multimorbidity. Such data might serve as the foundation for prediction-informed actions that enhance population health and lower expensive healthcare expenses.

Pre-diagnosis of T2D

In the period prior to an individual receiving a T2D diagnosis, we found a steadily increasing prevalence of hypertension (higher than in the control group), along with less severe but still substantial manifestations of ischaemic heart disease and documented renal illness. The incidence of asthma also increased. The prevalence of chest infections as well as ear, nose and throat infections increased in both groups. These findings imply that other health problems emerge that are precursors to the future emergence of T2D and that there is therefore a window of opportunity prior to the diagnosis of T2D when enhanced preventative interventions could be provided. The answer to the question of whether some pre-T2D diagnostic characteristics are a direct result of the beginning phase of diabetes or a side effect of the undetected onset of diabetes is crucial.

Consequently, it is only reasonable to assume that certain clinical indications associated with T2D would be present in patients who eventually receive a clinical diagnosis of T2D when utilising the strict cutoff of "clinical diagnosis" [24] as a time point. The duration of the pre-diagnosis time window in relation to the accumulation of comorbidities appears to be much longer than generally appreciated, particularly in terms of increasing levels of hypertension and an increased frequency of respiratory/ear, nose and throat infections and diagnosed asthma. While some indicators of impaired glucose control would be expected prior to diagnosis, these two observations stood out as being immediately of interest.

In general practice, hypertension is regularly acknowledged and treated as a risk factor for T2D due to its rising frequency among people who also exhibit other risk factors (such as obesity, sedentary lifestyles and smoking). It is less acknowledged that asthma attacks and related inflammation occur more often. Numerous studies have been conducted on the link between T2D and hypertension [25]. It is acknowledged that persistently high blood glucose levels can affect the vascular endothelium and other tissues, which may then lead to a rise in insulin resistance and an increased risk of cardiovascular disease. [2, 26, 27]. A considerable amount of research has focused on how insulin resistance and hypertension might be seen as precursors to the eventual onset of T2D [28, 29]. The authors of one study also observed that structural relationship changes observed in healthy individuals appear earlier in people with diabetes [30].

Despite all of the experimental and epidemiological evidence, the prediction models for the chance that any particular person would acquire T2D are still in the development stage [31]. Less is known and been published on the relationship between acute and chronic infections and T2D [32]. It is common knowledge that people with T2D have decreased immunity, albeit occasionally compounded by peripheral neuropathy and slowed skin healing processes. Compared to people who do not acquire diabetes, a higher percentage of those with T2D had respiratory infections before receiving a diagnosis [33]. However, in those with higher levels of endogenous diabetes risk factors, an enhanced involvement of inflammatory pathways in modifying insulin resistance [34] or impairing pancreatic beta-cell function [35] is still a possibility.

Understanding the underlying pathophysiological factors for the development of T2D necessitates the observation of asthma as a diagnosis in many people in the years prior to the diagnosis of T2D. Previous research has shown that inflammation brought on by underlying autoimmune diseases may be responsible for both the development of asthma and the later emergence of T2D [36]. Given that an increase in the diagnosis of asthma was also shown in our study, this may have some fundamental relationship to the existence of persistent underlying inflammations.

Post-diagnosis of T2D

In the period following the individual receiving a T2D diagnosis, we observed a steady increase in the diagnosis of renal disorder and ischaemic disease, along with the progressive onset of diabetic retinopathy as a manifestation of microvascular disease [37] and heart failure (manifestation of microvascular and

macrovascular disease [38]), with an eventual plateauing of hypertension at 68% of cases and RTI at 73% of cases. Numerous infections of the respiratory tract and elsewhere multiplied after a T2D diagnosis, which is a sign that continuous dysglycaemia has impaired the immune system's capacity to recognise and combat bacterial pathogens that enter the body [39, 40]. We do not believe that the degree of contact with medical services would necessarily have resulted in bias to the results.

A key question is whether the large variability in multimorbidity that we describe here results from the presence of shared risk factors for several diseases or from the harm one disease state causes contributing to the emergence of another. The importance of length, time and age, in conjunction with the functioning of the biological clock at the tissue level and how this is modified by genetic and epigenetic variables, are further considerations [41].

The pre-diagnostic period provides an opportunity to intervene with lifestyle and potentially pharmacological measures if people most at risk of developing T2D can be identified through application of a predictive risk score—not when they have already developed nondiabetic hyperglycaemia but many years before any degree of hyperglycaemia becomes apparent. Epidrugs are currently available that can modify DNA methylation and although these lack specificity at the present time, in the future they could provide therapies for a variety of complex illnesses [42, 43].

Finally, with this study, we have built on the findings of our previous paper [15] with a much larger cohort (eightfold larger) taken from across the conurbation of Greater Manchester, while also examining the relation between sociodemographic situation and longitudinal health outcomes in relation to cardiac conditions and lower RTIs. In this context, it has been suggested that inflammatory disorders and, in particular, infectious diseases increase the risk of T2D [44].

Strengths and Limitations

Diagnoses from all stages of the person's life have been considered. The DARE study, with its design and funding fully supported by the UK National Institute for Health and Care Research (NIHR), recruited people with diabetes (type 1 diabetes and T2D) and non-diabetes individuals from the same community and demographic situation across England. Thus, the sampling frame was representative of the English population at the time. However, the first drawback to our study is that the cohort analysed is small and that the analysis depends on the accuracy of the coding at the level of GP. The way that coding of diagnosis is done in primary care can mean that diagnosis data move forward in time because of recoding. Our diagnosis search did ask for the earliest time that a specific diagnosis was made.

Second, T2D is a diverse disorder, and we have not examined all its possible subgroups in the present study [3]. Third, the actual year of diagnosis with T2D may be several years after the onset of hyperglycaemia [45] because often above-normal glucose levels are not associated with any symptoms. Fourth, we discovered that the T2D person's average Townsend index was a sign of increased socioeconomic poverty; some clustering of multimorbidity prior to and following T2D diagnosis may thus be related to demographic considerations. Fifth, there is the potential, as in all primary care data-based studies, for bias through misclassification/missing data.

Finally, in relation to sample size, we accept that the sample size is small. Given the wide geographical spread of the DARE study and the duration of the follow-up that has been enabled through active ethical permission, we anticipate being able to extend the study to much larger numbers in due course.

CONCLUSION

In conclusion, our study demonstrates that subacute inflammation which manifests as the onset of asthma or an acute infection, regardless of whether it is caused by the genome, demography or comorbidities, may serve as a precursor to the later onset of T2D. The first diagnosis in many people is hypertension. These observations offer a fascinating and fresh perspective on the beginning and normal development from pre-T2D to

T2D diagnosis and beyond, implying a possible early stage of disease activity that is linked to but not yet clinically diagnosed as diabetes. The matter of metabolic control and how this relates to a broad range of treatment factors (pharmacological and non-pharmacological) will be addressed in a future work.

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Author Contributions. Adrian Heald, John Warner-Levy and Kevin McCay led on the writing of this paper. Rui Qin undertook the data analysis and generated the plots shown in the paper. Simon G. Anderson, Richard Williams and YonHong Peng advised on the data analysis. Ram Prakash Narayanan, Israel Fernandez, J. Martin Gibson provided input in relation to the context and interpretation of the findings. William Ollier provided senior oversight. All authors contributed to the final version of the manuscript and have approved it.

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Data Availability. The data that supports the findings of the study are not publicly available due to privacy restrictions. However, extracts of data will be made available to researchers on reasonable request. Adrian Heald is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations

Conflict of interest. No authors have any conflict of interest.

Ethical Approval. All participants gave explicit permission for their prospective health records to be interrogated. Ethical permission for access to the prospective health records for DARE study participants is extant until 2043 [16]. Data access for the project was approved and overseen by Health Innovation Manchester with reference number RQ019 (data approval 02/06/2022). The study was in accordance with the Declaration of Helsinki and was approved by Health Innovation Manchester.

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