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Assessment of greenhouse gas emission of type 2 diabetes management in adults: a modelling study in the UK

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ABSTRACT

Background The carbon footprint of end-to-end healthcare deliveries by the National Health Service in England totalled 25.0 megatons of carbon dioxide equivalent (CO_2e) in 2019. Optimal and sustainable healthcare can lead to better health outcomes as well as a lower environmental footprint.

Objectives To evaluate the potential impact of prevention and effective management of type 2 diabetes mellitus (T2DM) in adults on both the clinical outcomes and greenhouse gas (GHG) emissions in the UK healthcare setting.

Research design and methods We incorporated an environmental module into the existing IQVIA core diabetes model to estimate the impact of improving clinical outcomes on GHG emissions over a lifetime horizon. We assessed two hypothetical scenarios: (1) preventing progression from pre-diabetes to T2DM through diet and exercise versus no intervention and natural disease progression to T2DM; and (2) well-controlled T2DM using interventions with clinical benefit on glycosylated haemoglobin (HbA1c), and renal and cardiovascular outcomes versus uncontrolled T2DM.

Results Preventing progression to T2DM led to 6.357 additional undiscounted life years and 67% less kg CO_2e emissions compared with subsequent natural progression to T2DM for a person with pre-diabetes over a lifetime (emissions of 9586 kg CO_2e over 37.115 years vs 28 716 kg CO_2e over 30.758 years, respectively). Well-controlled T2DM led to 1.947 additional undiscounted life years and 21% less kg CO_2e emissions per patient over a lifetime compared with uncontrolled T2DM (emissions of 14 545 kg CO_2e over 22.772 years vs 18 516 kg CO_2e over 20.825 years, respectively). In both scenarios, the GHG emission savings were primarily due to reduced emissions related to avoidance of treating complications of T2DM including cardiovascular, renal and eye diseases.

Conclusion Effective prevention and management of T2DM through implementation of evidence-based clinical guidelines can improve patient outcomes while reducing the healthcare-related environmental impacts.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study incorporated an environmental module to the previously validated IQVIA core diabetes model V10.0.
⇒ For the model inputs, the efficacy data were sourced from phase III trials and the model applied additional glycosylated haemoglobin (HbA1c)-independent cardiorenal benefits.
⇒ Additionally, the model accounted for greenhouse gas emissions of pharmaceuticals to provide a more comprehensive environmental impact.
⇒ The model outcomes were reported using the metric incremental carbon footprint effectiveness ratio to reflect on the estimated environmental 'cost' of healthcare services associated with the care pathway of type 2 diabetes.
⇒ The study notes an overall lack of robust methodologies to determine greenhouse gas emissions associated with various therapeutics and the management of complications.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) accounts for nearly 90% of all cases of diabetes worldwide.[1] In 2021, 537 million adults had diabetes globally, a number expected to rise to 783 million by 2045.[1] In the UK, diabetes cases are projected to increase from 3.99 million in 2021 to 4.41 million by 2045.[1] Diabetes or its complications caused approximately 6.7 million deaths globally in 2021, including over 140 000 deaths in the UK.[1] T2DM incurs substantial direct and indirect cost burden to the patients, healthcare systems and society. The total cost burden of T2DM to the National Health Service (NHS) in the UK for 2021/22 was around £14 billion (€16 billion, US$18.7 billion), with £10.7 billion (€12.3 billion, US$14.3 billion) in direct medical costs and £3.3 billion (€3.8, US$4.4) in indirect costs.[2] Diabetes-related complications add to the existing economic and clinical burden of T2DM.[1–3] Cardiovascular disease (CVD)

and chronic kidney disease (CKD) increase the risk of diabetes-related morbidity and mortality.[4 5]

T2DM and its complications can be delayed or prevented by using multifactorial lifestyle interventions.[6 7] Furthermore, disease progression can be managed through pharmacological therapies.[6 7] However, despite evidence-based clinical guidance, nearly one-third of people with T2DM in England (36%) and Wales (39%) fail to achieve the target glycosylated haemoglobin (HbA1c) of 7.5% (58 mmol/mol).[8] Therefore, preventative measures to slow the progression of T2DM and early initiation of therapeutic interventions could be important for preventing diabetes-related complications and achieving optimal disease control.[1]

Advancements in healthcare interventions come at a financial impact as well as a 'cost' to the environment. Prior studies have addressed and established health and financial outcomes of various management strategies of T2DM; however, not many have assessed the impact on the environment.[9–12] The end-to-end delivery of healthcare interventions largely improves individual lives but contributes to 5% of the world's total greenhouse gas (GHG) emissions.[13] Carbon dioxide (CO_2) is mostly used as a reference gas as around three-quarters of anthropogenic GHG emissions are made up of CO_2.[14] In 2019, the annual carbon footprint of the NHS in England was about 25 megatons of CO_2 equivalent (CO_2e), around 4% of the national GHG emissions.[15 16] Of this estimate, 62% arose from the supply chain, 24% from the delivery of care, and 10% from travel by patients, visitors and staff.[15] With growing awareness of the environmental impact of healthcare interventions, governments are taking steps to mitigate it. In line with the national legislation in the UK, the NHS has committed to achieving net zero emissions by 2040, with an ambition for an 80% reduction by 2028 to 2032, and has emphasised the importance of sustainable healthcare.[16–18]

To support the net zero target, it is important to identify disease prevention and optimal care strategies that can benefit both patient lives and the wider environment.[19] To this end, it is imperative to understand the trade-off of health and environmental impact associated with optimal management of T2DM compared with poor management. Additionally, as lifestyle changes are a cornerstone of T2DM management, it is of interest to investigate the significance of sustainable preventive strategies. Therefore, this study evaluated the potential impact of (1) effective prevention of T2DM in adults with pre-diabetes, and (2) effective disease management in adults with T2DM on both the clinical outcomes and the GHG emissions in the UK healthcare setting.

METHODS

Modelling approach

We utilised the framework of the IQVIA core diabetes model (CDM) V10.0, which was adapted to include an environmental module by replacing the cost inputs with GHG emissions associated with medical interventions and procedures for management of T2DM and its complications.[20] The CDM and its validation studies have been documented in the literature.[20–22]

A cohort of 1000 individuals was selected for the simulation, with this sample size informed by previous literature.[17 23–25] Each patient was simulated 1000 times to achieve stability. The analysis was conducted over a lifetime horizon of 50 years.

An annual discount rate of 3.5% for health effects[26] and 0% for environmental effects (as all GHG emissions are valued equally to maintain intergenerational equity) were used.[27] Quality-adjusted life years (QALYs) were discounted because they reflect individual patient outcomes, whereas GHG emissions have intergenerational, population-wide implications, justifying the use of undiscounted values.[27] A non-specific mortality approach was applied using the 2020 single-year life tables for the UK and the 2022 mortality statistics.[28 29]

Current care pathway and scenarios

The current care pathway for T2DM includes an individualised approach to care by the National Institute for Health and Care Excellence (NICE), including lifestyle interventions and pharmacological advice.[7 30] Metformin is the preferred first-line drug treatment for T2DM, or a sodium-glucose co-transporter-2 inhibitor (SGLT2i) alone if metformin is contraindicated. For treatment intensification, SGLT2i, dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RA) are considered. The GLP-1 RAs and first-line SGLT2i are recommended for patients with T2DM with established CVD, CKD or those with a high risk of developing CKD.[7 31] When glycaemic control is inadequate despite treatment, insulin-based therapy is suggested (with or without other drugs).[7] Based on the NICE current care pathway, the impact of T2DM interventions on clinical and GHG emission outcomes were assessed under the following two hypothetical scenarios:

1. Scenario 1 (prevention of T2DM): In this scenario, the target patient population was adults with pre-diabetes, aged ≥40.0 years. The model assumed two management pathways for this population: (1) people receiving diet and exercise advice from a nutritionist for 4 years (and adhered to for lifetime) and not progressing to T2DM (intervention arm); and (2) people not receiving nutritionist advice and naturally progressed to T2DM (comparator arm). The nutritionist's advice for 4 years in the intervention arm was assumed based on a subgroup analysis in a Cochrane review of impact of diet and physical activity on prevention or delay of T2DM.[32] In the intervention arm, we assumed that HbA1c remained below 6.5% without any further progression to T2DM during lifetime for all individuals. Individuals in the comparator arm were assumed to receive three lines of anti-diabetic therapy: first-line metformin, second-line metformin+DPP4 inhibitor, and third-line basal+bolus insulin.

2. Scenario 2 (well-controlled T2DM): In this scenario, the target patient population was adults with T2DM, aged ≥54.5 years, based on a pivotal DPP4 inhibitor trial in patients with uncontrolled T2DM on metformin alone.[33] The model assumed two treatment pathways for this population: (1) patients receiving timely and effective diabetes treatment (intervention arm: well-controlled T2DM); and (2) patients who did not receive this treatment (comparator arm: uncontrolled T2DM). Based on the trial, background metformin therapy was allowed for all patients. The model defined well-controlled T2DM with an HbA1c decreasing to and remaining constant at <6.5% for lifetime irrespective of therapy given, and additional HbA1c-independent cardiorenal benefits provided by the full suite of guideline-recommended medical therapies.[34–36] For the comparator arm, HbA1c increased up to 9% as per natural disease progression based on the UK Prospective Diabetes Study (UKPDS) 68 risk equation for HbA1c.

Model inputs and sources

Baseline population characteristics

In scenario 1, the baseline characteristics for people with pre-diabetes (intervention arm) were sourced from a trial evaluating the efficacy of interventions to promote a healthy diet and physical activity in individuals with impaired glucose tolerance in the UK.[37] These individuals were assumed to not have any baseline CVD or CKD complications based on the trial. For people who naturally progressed to T2DM (comparator arm), it was not possible to add a new health state for this progression; therefore, all outputs and emissions were calculated from the time after T2DM was diagnosed. For these individuals, the baseline characteristics were based on a study evaluating the efficacy and safety of a DPP4 inhibitor as an add-on therapy to metformin in patients with T2DM uncontrolled on metformin (online supplemental table S1).[33]

For scenario 2, the baseline characteristics were based on the same DPP4 inhibitor study, assuming that this patient group represented an overall population with early-stage T2DM in the real world (online supplemental table S2).[33] Missing data for the baseline complications was populated using the CDM default values.

Clinical inputs and utilities

In the first scenario, no change was assumed for HbA1c for the intervention arm throughout the model time horizon. In the comparator arm, efficacy data in terms of HbA1c, blood pressure, lipid levels and body mass index for the three lines of treatment were sourced from the metformin prescribing label and published literature for other anti-diabetes medications (online supplemental table S3).[33 38]

For the second scenario, treatment-related change in HbA1c for the intervention arm was sourced from a GLP-1 RA trial (SURPASS-1) (online supplemental table S4).[39] Efficacy data for other parameters were based on the DPP4 inhibitor trial by Charbonnel *et al*.[33] Efficacy data on all outcomes for the comparator arm (assumed on placebo+metformin) were obtained from the same DPP4 inhibitor trial.[33] Meta-analyses of the cardiovascular outcome trials suggest that GLA-1RA and SGLT-2 inhibitors provide additional benefits on cardiovascular and renal outcomes independent of the effects mediated through HbA1c. These additional CVD (relative risk (RR) of heart failure, myocardial infarction and stroke) and CKD (estimated glomerular filtration rate (eGFR) reduction, and RRs for microalbuminuria, gross renal proteinuria and end-stage renal disease) benefits were applied for the intervention arm and were retrieved from the meta-analyses.[34–36] Rates of non-severe hypoglycaemic event and severe hypoglycaemic event were sourced from previous publications.[38 40] The eGFR progression for the intervention arm was predicted based on the Chronic Renal Insufficiency Cohort (CRIC) Study.[41]

People with pre-diabetes who did not progress to T2DM were assumed to not develop any complications due to T2DM. However, they could develop CVD and CKD complications based on the Framingham Heart Study risk equation, based on their age and baseline characteristics. The cardiovascular risk in the model was predicted using the UKPDS 68 (for first scenario) or UKPDS 82 (for second scenario) risk equations.[42 43] For both scenarios, the health-related quality of life utilities associated with each diabetes-related complication were informed by a systematic review of utilities,[44] and the disutilities due to hypoglycaemic events were retrieved from Foos and McEwan.[45]

GHG emission inputs

The GHG emissions associated with diabetes and T2DM were estimated based on the avoidance of ongoing pharmaceutical management and anticipated complications in the absence of appropriate interventions. An assessment of procedures, medications and travel components within each intervention and complication was conducted to assess key contributors to GHG emissions. Two primary estimation approaches were employed for collecting the GHG emission inputs—(1) resource-based and (2) cost-based—with a preference for the former due to a more robust estimation by encompassing both direct and indirect emissions across diverse healthcare services and procedures. Among multiple resource-based estimations, sources providing the most comprehensive coverage of the patient care pathway were prioritised.

In the 'resource-based approach', GHG emissions for an event or treatment were directly obtained from previously published sources. The 'cost-based approach' calculates total GHG emission for a procedure/event by multiplying its estimated cost with a carbon intensity factor, which is an estimate of the average kg CO_2 emissions emitted per £ spent delivering health services.[46] For most calculations, a carbon intensity factor of 0.23 kg CO_2e/£ was used, except for blood glucose tests where a value of 3 kg CO_2e/£ was

used.[46 47] We prioritised a resource-based approach for our analysis over a cost-based approach as it is more granular.[17 46] Overall, two-thirds of the GHG emission values were captured through the resource-based approach. Wherever the cost-based approach was applied, unit costs (direct medical costs and cost of managing complications) were collected from published literature and UK national sources (online supplemental table S5).

GHG emissions associated with pharmaceuticals are primarily influenced by molecular weight and the number of synthesis steps involved in their manufacturing. Due to limited published data on complexity associated with molecular synthesis, a high-level approach was adopted to classify molecules based on complexity into low, medium or high complexity. Emission estimates for each category were derived by leveraging data from Parvatker *et al*, which analysed 20 molecules accounting for the active pharmaceutical ingredient only, and excluding excipients, packaging or delivery systems.[48] Emissions for simpler molecules ranged from 10 to 100 kg CO_2e/kg, while those for medium to high complexity molecules ranged from 100 to 1500 kg CO_2e/kg. These estimates were further triangulated using the Association of the British Pharmaceutical Industry carbon footprint tool, which reports emissions of 600 and 1500 kg CO_2e/kg for low and medium complexity molecules, respectively.[49] Finally, the values of 50 and 1000 kg CO_2e/kg were adopted to represent emissions from low (such as metformin and aspirin) and medium (such as injectable drugs) complexity molecules, respectively.

Model analysis

Model outcomes

Clinical outcomes were reported using per-patient life years (LYs) and quality-adjusted life years (QALYs), and event rates of diabetes-related complications. Environmental impact was reported using per-patient GHG emission (kg CO_2e: lifetime, annualised and year-on-year) which was then converted to incremental carbon footprint effectiveness ratio (ICFER), ie, the change in cumulative carbon footprint over QALYs gained (kg CO_2e/QALY gained).[50] The ICFER helps examine balancing future health choices with their impact on the environment. Although there is no established threshold

Table 1 GHG emission-effectiveness analysis results (per patient) for prevention of T2DM and well-controlled T2DM populations in the UK

	Values, mean (95% CI)		Incremental values
Parameters	**Pre-diabetes, no progression**	**Diabetes, naturally progressed**	**Pre-diabetes, no progression vs diabetes, naturally progressed**
LYs (years), undiscounted	37.115 (37.092 to 37.138)	30.758 (30.728 to 30.787)	6.357 (NC)
LYs (years), discounted	20.482 (20.473 to 20.491)	17.732 (17.718 to 17.745)	2.750 (2.735 to 2.766)
QALYs, discounted	15.409 (15.402 to 15.415)	11.662 (11.653 to 11.671)	3.747 (3.736 to 3.757)
Total GHG emission (kg CO_2e)	9586 (9560 to 9612)	28 716 (28 652 to 28 779)	−19 129 (−19 199 to −19 060) (−66.6%)
ICFER (kg CO_2e/QALY)	Dominant		
	Well-controlled T2DM	**Uncontrolled T2DM**	**Well-controlled vs uncontrolled T2DM**
LYs (years), undiscounted	22.772 (22.749 to 22.796)	20.825 (20.803 to 20.848)	1.947 (NC)
LYs (years), discounted	14.848 (14.835 to 14.860)	13.965 (13.953 to 13.977)	0.883 (0.866 to 0.899)
QALYs, discounted	10.295 (10.286 to 10.304)	9.561 (9.552 to 9.569)	0.734 (0.722 to 0.746)
Total GHG emission (kg CO_2e)	14 545 (14 504 to 14 585)	18 516 (18 471 to 18 561)	−3972 (−4030 to −3913) (−21.4%)
ICFER (kg CO_2e/QALY)	Dominant		

Percent values in parentheses represent the percentage of improvement in (reduction in) GHG emission in pre-diabetes vs naturally progressed or well-controlled vs uncontrolled T2DM.
CO_2e, carbon dioxide equivalent; GHG, greenhouse gas; ICFER, incremental carbon footprint effectiveness ratio; LYs, life years; NC, not calculated; QALYs, quality-adjusted life years; T2DM, type 2 diabetes mellitus.

for ICFER, a dominant value indicates that health gains are achieved at a reduced environmental impact.[50 51] The 95% confidence interval (95% CI) values as generated by the model were used to describe the range of values.

As people with pre-diabetes who do not progress to T2DM and those with well-controlled T2DM were expected to live longer and continue contributing towards GHG emission, annualised GHG emission (kg CO_2e per patient life-year) was calculated to understand the impact of this difference in survival.

Sensitivity analysis

Deterministic sensitivity analysis for the second scenario: The first sensitivity analysis was conducted to evaluate the impact of therapy in patients with T2DM and CKD who were elderly with higher comorbidities compared with uncontrolled T2DM. The baseline characteristics were derived from a phase III trial in patients with T2DM and CKD (online supplemental table S6).[52] For the second sensitivity analysis, we tested the impact of a 2- or 5-year delay in starting effective therapy for T2DM in patients with well-controlled T2DM which reduced the HbA1c to <6.5% and continued for their lifetime.

In the model base case, health effects were discounted but environmental effects were not. To address the potential bias that may arise due to this, deterministic sensitivity analyses were conducted for both scenarios which included undiscounted health effects and undiscounted environmental effects.

One-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA) were conducted for each of the two scenarios to identify the key variables that influenced environmental and clinical outcomes.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Prevention of T2DM

Preventing progression of pre-diabetes to T2DM improved undiscounted LYs (6.357) and QALYs (3.747) compared with natural progression to T2DM in the UK healthcare setting over a lifetime horizon (table 1). People who remained prediabetic had lower diabetes-related complication or event rates (244 vs 60 167 events per 100 patients over lifetime) in comparison to patients with natural progression to T2DM (online supplemental figure S1A), specifically renal (73% less events) and eye diseases (59% less events) (online supplemental table S7). The cumulative incidence of CVD complications was modestly higher in people who remained pre-diabetic (11% more cumulative events).

The total GHG emission associated with care of people with pre-diabetes and no progression was 67% less (19 129 kg CO_2e over lifetime) than those who naturally progressed to T2DM (table 1). This reduction in GHG emissions was driven mainly by the reduced need for management of diabetes-related complications, primarily CVD (35.8%), renal (97.6%) and eye diseases (73.3%), over lifetime as well as the avoidance of T2DM treatment (88.4% decrease) (figure 1A). A modest increase in GHG emissions was seen for disease management (20.5% kg CO_2e) in people who remained pre-diabetic. This difference in GHG emission due to disease management became negligible when annualised savings were estimated (figure 2A). The overall annualised savings

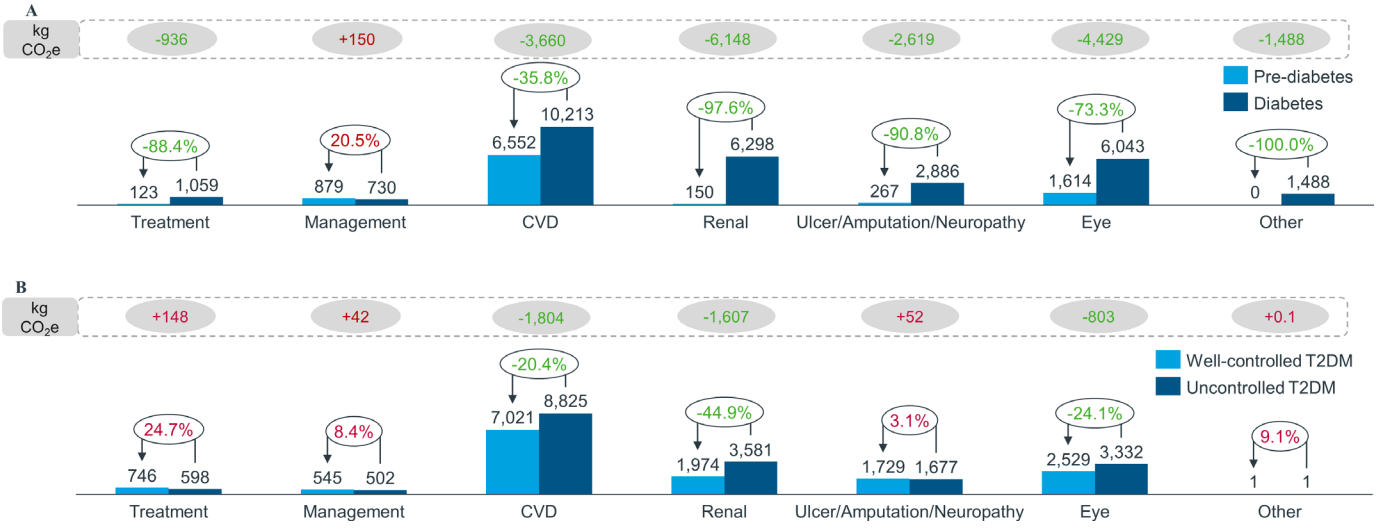

Figure 1 Driving factors for reduction in GHG emissions per patient over lifetime. (A) Prevention of T2DM and (B) well-controlled T2DM. 'Other' category includes non-severe hypoglycaemia events, severe hypoglycaemia events not requiring medical assistance and severe hypoglycaemia events requiring medical assistance. Components of management-related GHG emissions include concomitant medications (statins, ACE inhibitors and so on), screening and patient management. CO_2e, carbon dioxide equivalent; CVD, cardiovascular diseases; GHG, greenhouse gas; T2DM, type 2 diabetes mellitus.

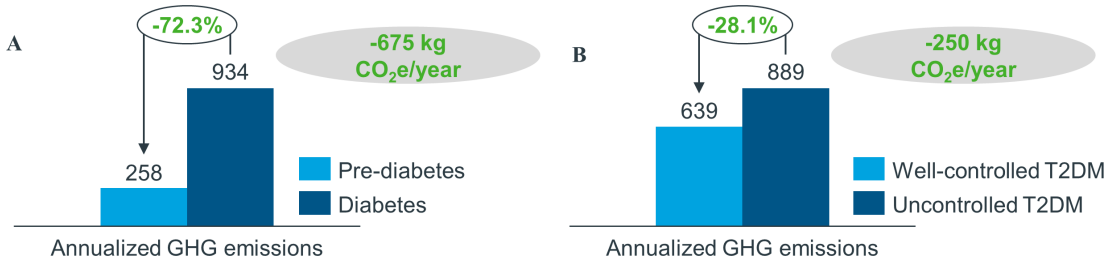

Figure 2 Annualised GHG emissions per patient life-year. (A) Prevention of T2DM and (B) well-controlled T2DM. CO_2e, carbon dioxide equivalent; GHG, greenhouse gas; T2DM, type 2 diabetes mellitus.

were higher (72%) than those with lifetime GHG emission savings (67%).

Well-controlled T2DM

An average patient with well-controlled T2DM was estimated to have improved undiscounted LYs (1.947) and QALYs (0.734) compared with a patient with uncontrolled T2DM in the UK healthcare setting over a lifetime horizon (table 1). Well-controlled T2DM conferred a lower risk of developing diabetes-related events in comparison to uncontrolled T2DM (307 vs 473 events per 100 patients over lifetime) (online supplemental figure S1B). The major factors driving this reduced incidence of diabetes-related events were renal (75% fewer events), eye (57% fewer events), and CVD complications (30% fewer events) (online supplemental table S8).

Care for a patient with well-controlled T2DM was associated with 21% less GHG emission (3972 kg CO_2e) compared with a patient with uncontrolled T2DM over lifetime (table 1). This reduction in GHG emissions was mainly driven by reduced emissions for managing renal (44.9%), CVD (20.4%) and eye diseases (24.1%). Slightly higher GHG emissions were observed for T2DM treatment (25.0%) and secondary risk management (8.4%) in people with well-controlled T2DM (figure 1B). The annualised savings in GHG emissions for well-controlled versus uncontrolled T2DM was slightly higher than those observed for the lifetime savings (28% vs 21%) (figure 2B). When year-on-year GHG emissions were analysed, effective therapy for well-controlled T2DM resulted in savings as early as year 1 (3% savings) and reached 21% at 23 years after the start of therapy (ie, average life expectancy of a well-controlled T2DM patient) (online supplemental figure 2A). The peak savings in year-on-year cumulative GHG emissions due to renal events was 40% at year 27 (online supplemental figure S3A) and savings due to CVD events was 22% at year 25 (online supplemental figure S4A).

Sensitivity analysis

T2DM with CKD (well-controlled T2DM)

Effective treatment of patients with T2DM with CKD resulted in gain in undiscounted LYs (2.148) and QALYs (0.900) compared with patients with uncontrolled T2DM (table 2). As these patients had baseline CKD, they experienced an increased number of CVD complications which decreased overall savings in GHG emissions (online supplemental table S9). Optimal management of T2DM with CKD also resulted in savings in GHG emissions (18.8%) over lifetime compared with patients with uncontrolled T2DM (table 2). When comparing these results to patients with only T2DM, the gain in LYs (2.148 vs 1.947) was higher while the savings in GHG emissions were slightly lower (18.8% vs 21.4%) (figure 3A,B).

The year-on-year analysis of GHG emissions in patients with T2DM with CKD showed that the savings start as early as year 1 (10%) and peak at 25% at 11 years after the start of therapy, slightly higher than those seen in patients without CKD (21% at year 23) (online supplemental figure S2A,2B). The year-on-year GHG emission savings for renal complications were observed from year 1 (66% savings) with a peak of 70% by year 4 post treatment initiation, which remained high throughout the patient's lifetime (online supplemental figure S3B). As observed with lifetime GHG emission savings, the year-on-year savings in GHG emission due to CVD events were much lower than those seen in patients with T2DM alone, with an average of 8% savings, reaching 9% at year 5 (online supplemental figure S4B).

Delay in initiating effective therapy (well-controlled T2DM)

Delay of 2 or 5 years in starting effective treatment and achieving optimal control of T2DM decreased the undiscounted LYs of patients when compared with patients with non-delayed treatment initiation (22.772 for non-delayed vs 22.596 for 2-year delay vs 22.397 for 5-year delay) (table 2). Moreover, GHG emissions over lifetime associated with well-controlled T2DM increased with the delaying of effective treatment (14 545 for non-delayed vs 14 819 for 2-year delay vs 15 459 for 5-year delay) (figure 3C and table 2). Still, compared with uncontrolled T2DM, GHG emission was less for well-controlled T2DM even with a 2- or 5-year delay in treatment initiation (20.0% or 16.5% reduction) (table 2). The year-on-year GHG emission savings for well-controlled T2DM start in year 3 or year 5 when the effective treatment was initiated in the 2-year or 5-year delay scenario, respectively (online supplemental figures S2–S4).

With a 2-year delay in initiating treatment, the peak savings of 20% in year-on-year GHG emissions were achieved at year 25 (online supplemental figure S2C). The year-on-year GHG emissions savings due to renal diseases in well-controlled versus uncontrolled patients

Table 2 GHG emission-effectiveness analysis results (per patient) for well-controlled T2DM population in the UK (sensitivity analysis)

Parameters	Values (95% CI)		Incremental values
	Well-controlled T2DM	Uncontrolled T2DM	Well-controlled vs uncontrolled T2DM
T2DM with CKD			
LYs (years), undiscounted	14.506 (14.488 to 14.525)	12.358 (12.340 to 12.376)	2.148 (NC)
LYs (years), discounted	10.755 (10.744 to 10.767)	9.516 (9.505 to 9.527)	1.239 (1.223 to 1.255)
QALYs, discounted	7.119 (7.111 to 7.127)	6.219 (6.211 to 6.226)	0.900 (0.889 to 0.911)
Total GHG emission (kg CO_2e)	17 267 (17 227 to 17 306)	21 258 (21 210 to 21 306)	–3992 (–4054 to –3929) (–18.8%)
ICFER (kg CO_2e/ QALY)	Dominant		
2-year delay in effective treatment			
LYs (years), undiscounted	22.596 (22.57 to 22.621)	20.825 (20.803 to 20.848)	1.771 (NC)
LYs (years), discounted	14.748 (14.735 to 14.761)	13.965 (13.953 to 13.977)	0.783 (0.766 to 0.800)
QALYs, discounted	10.201 (10.192 to 10.210)	9.561 (9.552 to 9.569)	0.640 (0.628 to 0.653)
Total GHG emission (kg CO_2e)	14 819 (14 779 to 14 859)	18 516 (18 471 to 18 561)	–3698 (–3757 to –3639) (–20.0%)
ICFER (kg CO_2e/ QALY)	Dominant		
5-year delay in effective treatment			
LYs (years), undiscounted	22.397 (22.374 to 22.420)	20.825 (20.803 to 20.848)	1.572 (NC)
LYs (years), discounted	14.642 (14.630 to 14.654)	13.965 (13.953 to 13.977)	0.677 (0.659 to 0.695)
QALYs, discounted	10.094 (10.086 to 10.103)	9.561 (9.552 to 9.569)	0.534 (0.521 to 0.547)
Total GHG emission (kg CO_2e)	15 459 (15 417 to 15 501)	18 516 (18 471 to 18 561)	–3057 (–3118 to –2996) (–16.5%)
ICFER (kg CO_2e/ QALY)	Dominant		

Percent values in parentheses represent the percentage of improvement in (reduction in) GHG emission in well-controlled vs uncontrolled T2DM.
CKD, chronic kidney disease; CO_2e, carbon dioxide equivalent; GHG, greenhouse gas; ICFER, incremental carbon footprint effectiveness ratio; LYs, life years; NC, not calculated; QALYs, quality-adjusted life years; T2DM, type 2 diabetes mellitus.

were 1% at year 3 and reached 38% by 26 years after treatment initiation (online supplemental figure S3C). A 2-year delay in the start of effective therapy also resulted in lower peak year-on-year GHG emission savings due to CVD events compared with immediate start (21% vs 22%) (online supplemental figure S4C).

With a 5-year delay in initiating treatment, the peak GHG emission savings of 15% were achieved at year 22 (online supplemental figure S2C). The year-on-year GHG emissions savings due to renal diseases in well-controlled versus uncontrolled patients were 1% at year 2 and reached 36% by 28 years after treatment initiation (online supplemental figure S3C). A 5-year delay in the start of effective therapy also resulted in lower peak year-on-year GHG emission savings due to CVD events compared with the non-delayed scenario (17% vs 22%) (online supplemental figure S4C).

Undiscounted QALYs and GHG emissions

The base case results were found to be robust when undiscounted QALYs were used. In both scenarios, incremental undiscounted QALYs were higher than incremental discounted QALYs (scenario 1: 1.555 vs 0.734; scenario 2: 7.618 vs 3.747) (online supplemental table S10). The

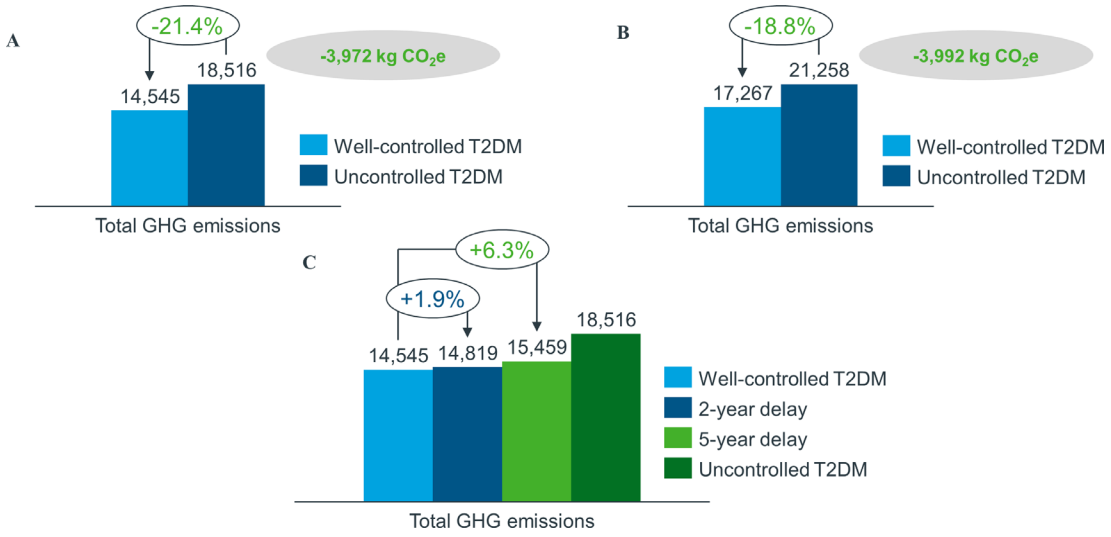

Figure 3 Total cumulative lifetime GHG emissions in well-controlled vs uncontrolled T2DM patient. (A) T2DM, (B) T2DM with CKD and (C) T2DM with 2- or 5-year delay in effective therapy. CO_2e, carbon dioxide equivalent; GHG, greenhouse gas; T2DM, type 2 diabetes mellitus.

ICFER values for both scenarios showed that QALY gains were achieved at a reduced GHG emission.

OWSA and PSA

The OWSA and PSA analyses validated the robustness of base case results (online supplemental tables S11–S13 and figures S5,S6.

DISCUSSION

This study highlighted that (1) prevention of T2DM through diet and exercise in adults with pre-diabetes, and (2) optimal control of disease in adults with T2DM, can improve patient outcomes (LYs and QALYs) while also reducing the environmental footprint over a lifetime horizon. These findings strengthen the rationale for preventing progression of pre-diabetes to T2DM and effective management of T2DM and its complications, especially cardiovascular and renal diseases in the UK healthcare setting.

In the first scenario, preventing progression of pre-diabetes to T2DM through diet and exercise improved survival, decreased complications (except CVD) and reduced GHG emissions by more than half over lifetime compared with patients who naturally progressed to T2DM. Since older age confers an increased risk of CVD events independent of HbA1c progression (based on the Framingham CVD risk equation),[53] the cumulative incidence of CVD complications was modestly higher in people with pre-diabetes without progression who lived ~6 years longer.

In the second scenario, optimal control of T2DM with effective treatment improved LYs, decreased complication rates and reduced total GHG emission over lifetime compared with uncontrolled T2DM. In well-controlled T2DM patients, GHG emissions were higher for T2DM treatment and secondary risk management, emphasising that emissions cannot be completely negligible as long as patients require treatment. Rather, the emissions can be reduced using lower GHG emission alternatives, and by focusing on avoidable sources of GHG emissions such as disease complications.

A few prior studies have evaluated GHG emissions associated with the T2DM care pathway. The Sustainable Markets Initiative's T2DM case study highlights the impact of seven levers of change on reducing overall GHG emissions.[54] For a cohort of people with pre-diabetes, two low-cost interventions were modelled: (1) primary prevention (diet and exercise) reducing GHG emissions by 34%; and (2) disease management using mobile apps reducing GHG emissions by 5%.[54] Our study shows that diabetes preventive strategies or optimal disease management through guideline-directed medical therapy can improve patient clinical outcomes and reduce environmental impact. It is to be noted that we assumed that preventive strategies and treatment effects were maintained over lifetime, indicating the importance of treatment adherence by patients and timely treatment intensification by treating physicians.

A previous analysis of the environmental impact of the T2DM care pathway using IQVIA CDM showed that maintaining HbA1c at 7% reduces total kg CO_2e/patient by 18% in patients on first-line metformin and by 13% in patients on third-line therapy compared with those on placebo/no therapy.[17] Furthermore, savings in total kg CO_2e/patient was 12% or 9%, respectively, when 1% reduction in HbA1c was achieved using additional glucose-lowering treatments.[17] Our study estimated higher GHG emission savings (21% kg CO_2e) than this earlier analysis, which may be due to the differences in the approach used for estimation of GHG emission inputs and the assumptions on hypothetical scenarios. This earlier study did not include glucose-lowering interventions in the assessment

of GHG emissions, while we accounted for GHG emissions of pharmaceuticals to provide a more comprehensive environmental impact. Additionally, in our analysis, patients with well-controlled T2DM achieved an HbA1c of <6.5% for their lifetime compared with a fixed HbA1c of 7% in Fordham *et al*.[17] For uncontrolled T2DM, we assumed a capping of HbA1c at 9%, to avoid unrealistic projections, as patients approaching this threshold are typically treated to prevent further deterioration. This approach aligns with clinical practice, except in cases of severe non-adherence or specific comorbidities, which were not modelled in this study. Another strength of our study is that we sourced the efficacy impact from phase III trials and applied additional HbA1c-independent cardiorenal benefits, making our analysis more realistic.

However, we note a few limitations of this study. First, this study does not determine the statistical significance of reduced GHG emissions, a limitation commonly associated with health economic models. However, sensitivity analyses were performed by using alternate assumptions and input parameters which demonstrated the robustness of our results. Second, there is an overall lack of robust methodologies to determine GHG emissions associated with various therapeutics and the management of complications. Although we collected GHG emissions in a systematic manner to our best efforts, no published emission data were available for a few comorbidities and complications. Therefore, a cost-based approach was used as an alternative. Future studies to understand GHG emission of expensive and resource-intensive procedures are needed to address this evidence gap. Third, we could not capture GHG emission savings that would have been generated when people with pre-diabetes adopted a healthier lifestyle due to unavailability of data in the clinical studies. The GHG emission savings could potentially be higher if people with pre-diabetes had preferred walking or cycling rather than transportation or had opted for a plant-based diet over a meat-based diet. Fourth, treatment of T2DM can be very dynamic and individualised, especially in later lines of treatments. Cohort-based models, such as the IQIVA CDM, only model cohorts of patients with minimal heterogeneity. An individual-based model might be better able to capture the impact of individualised treatments. However, they rely heavily on extensively detailed model inputs and were not feasible for this study. Lastly, the cohort baseline characteristics relied on clinical trial populations, which is a common practice in health economic modelling. While these cohorts are representative of the trial populations, we acknowledge that they may not fully reflect real-world settings—although our sensitivity analysis of scenario 2 using a high-risk population of T2DM with CKD supported the base case results.

Besides these limitations, this study adds to the limited existing research that incorporates environmental assessments in a health economic model. While health economic modelling techniques are employed to evaluate the environmental impact of T2DM management, this study does not constitute a conventional economic evaluation, as healthcare costs are not included as an outcome. However, QALYs are included to address the survival paradox, where foregoing treatment may reduce GHG emissions but leads to premature mortality. Their inclusion ensures environmental impact is assessed alongside patient health outcomes. It is important to note that QALYs were discounted, whereas GHG emissions were not, reflecting their distinct temporal implications. QALYs pertain to individual patient outcomes, while GHG emissions exert intergenerational, population-wide effects, thereby justifying the use of undiscounted values for emissions.[27] This assumption was tested through sensitivity analysis, which presented both undiscounted QALYs and GHG emissions. The base case results remained robust when undiscounted QALYs were applied, with incremental undiscounted QALYs consistently higher than incremental discounted QALYs in both scenarios. Furthermore, this study utilises the metric ICFER to reflect on the estimated environmental 'cost' of healthcare services associated with the care pathway of T2DM under two scenarios which can possibly be used for decisions around policymaking. Although in all scenarios tested, we observed negative ICFERs (improved health outcomes at lower environmental impact), there is a possibility of scenarios which bring about a decrease in both environmental impact as well as health outcomes.[50 51] This raises the question of whether the policymakers will consider such trade-off of health for GHG emission reductions.

CONCLUSIONS

This study underscores that (1) effective prevention of T2DM through diet and exercise in adults with pre-diabetes, and (2) optimal disease management in adults with T2DM through early implementation of evidence-based recommendations, can improve patient outcomes and reduce the healthcare-related environmental impact. Reductions in the incidence of comorbidities (especially cardiovascular and renal events) are key to driving savings in GHG emissions.

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Competing interests NL is an employee and shareholder of Novo Nordisk. EM and JC are employees of AstraZeneca and may hold AstraZeneca stock. JV is employed by Roche and holds financial equities in Roche. AP is employed by GSK and holds financial equities in GSK. PdLT is an employee of Sanofi and holds financial stocks. JGi, MS, IC, GR, LT, SV, YL, WX, JGo, FA and KM have no conflict of interest to declare.

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