An Analysis of Diabetes Mortality and Morbidity Risk

Diabetes Working Party

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Title

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1 Abstract

People with diabetes, both type 1 and type 2, run a greater risk of developing one or more severe health complications, including cardiovascular disease and cerebrovascular disease. Diabetes is also a leading cause of blindness in working aged people. Life expectancy following a diagnosis of diabetes has historically been less than in those without diabetes given that inadequate glycaemic control gives rise to several complications that cause premature death.

However, in recent years, management of diabetes both from a personal as well as a physician-led perspective has improved such that survival with diabetes has significantly improved. New pharmaceuticals as well as enhanced monitoring have transformed the lives of people living with diabetes. Life expectancy with optimal glycaemic management has been extended in those with diabetes, however, the long-term impact of new pharmaceuticals has yet to be fully appreciated.

Research has also increased our understanding of the pathophysiology of the condition allowing for greater granularity when considering our approach to underwriting this condition.

2 Keywords

HbA1c:

A haemoglobin A1c (HbA1c) test measures the amount of blood sugar (glucose) attached to haemoglobin. Haemoglobin is the part of your red blood cells that carries oxygen from your lungs to the rest of your body. An HbA1c test shows what the average amount of glucose attached to haemoglobin has been over the past three months. It's a three-month average because that's typically how long a red blood cell lives. If you have diabetes, an ideal HbA1c level is 48mmol/mol (6.5%) or below. If you're at risk of developing type 2 diabetes, your target HbA1c level should be below 42mmol/mol (6%).

Sources : Diabetes UK, https://www.diabetes.org.uk/

National Library of Medicine, https://medlineplus.gov/lab-tests/hemoglobin-a1c-hba1c-test/

Prediabetes:

Prediabetes describes a condition in which the blood sugar level is higher than it should be but not high enough for a formal diagnosis of diabetes. It is also called impaired fasting glucose or impaired glucose tolerance. People with type 2 diabetes almost always had prediabetes first which for the most part is symptom-free.

Source: WebMD, https://www.webmd.com/diabetes/

“Various organizations have defined prediabetes with criteria that are not uniform. The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycaemia using two

specific parameters; impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and impaired glucose tolerance (IGT) defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 h oral glucose tolerance test (OGTT). The American Diabetes Association (ADA), on the other hand has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has additional haemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of prediabetes." (Bansal, 2015)

Impaired glucose tolerance (IGT):

Impaired glucose tolerance means that blood glucose is raised beyond normal levels, but not high enough to warrant a diabetes diagnosis.

Source : Diabetes UK, https://www.diabetes.org.uk/

Impaired fasting glucose (IFG):

Impaired fasting glycaemia occurs when blood glucose levels in the body are elevated during periods of fasting, but not enough to prompt a diagnosis of diabetes. Impaired fasting glycaemia (IFG) may also be known as prediabetes or metabolic syndrome.

Source : Diabetes UK, https://www.diabetes.org.uk/

Hypoglycaemia:

A low blood sugar level, also called hypoglycaemia or a "hypo", is where the level of sugar (glucose) in your blood drops too low. It mainly affects people with diabetes, especially if they take insulin. A low blood sugar level can be dangerous if it's not treated quickly, but you can usually treat it easily yourself.

Source: NHS UK, https://www.nhs.uk/conditions/low-blood-sugar-hypoglycaemia/

Hyperglycemia:

High blood sugar (hyperglycaemia) is where the level of sugar in your blood is too high. It mainly affects people with diabetes and can be serious if not treated.

Source: NHS UK, https://www.nhs.uk/conditions/high-blood-sugar-hyperglycaemia/

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3 Executive summary

The life insurance industry currently underwrites customers with diabetes on a range of factors based on medical expertise and various published studies. The work undertaken by the Diabetes Working Party (DWP) is to investigate mortality and morbidity risk associated with both type 1 and type 2 diabetes by conducting an extensive literature review. In addition, the DWP has conducted a global underwriting survey.

The DWP was also involved in initiating an important project commissioned by the IFoA's Actuarial Research Centre (ARC), Pacific Life Re, Partner Re, Swiss Re, Legal & General and Zurich Insurance Group. The research is being carried out by world-leading experts in risk analysis, risk modelling and risk evaluation at the University of Leicester, supported by the Real-World Evidence Centre and the Leicester Diabetes Centre, a unique, collaborative partnership between the NHS and the University of Leicester[1]. The output from this project will be published separately and is not within the scope of this paper.

The paper is structured as follows:

1. Literature review of type 1 and 2 covering mortality and morbidity risk
2. How does the industry underwrite people with diabetes across the UK/Ireland and Asia[2] (with a breakdown for Mainland China and the rest of Asia)?

The last decade has seen significant advances in treatments, particularly for Type 2 diabetes, with evidence of at least two different drug classes delivering benefits in glycaemic control for some people living with diabetes. The long-term impact of these drugs has yet to be fully appreciated, as currently available risk estimates are derived from data that is more than ten years old, prior to the widespread use of these medicines. A key aim of this research is to widen access to insurance products for customers with diabetes by improving data available to the insurance industry. This research will be of interest to those insurers/reinsurers that write protection and longevity products.

Diabetes is a leading cause of death globally and a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. The prevalence of diabetes is significant and is increasing rapidly. This makes diabetes (type 1 and type 2) an important topic for the insurance industry as well as in the wider public interest.

In summary:

1. Literature review

Table 1: summary of topics covered in literature review with key messages

Topic reviewed	Key messages
Diabetes and mortality (type 1 and type 2)	At the time of review, published analysis does not capture the impact of modern treatments, particularly for those with type 2 diabetes. Based on published research, people with diabetes are at an increased risk of higher morbidity and excess mortality compared to the general population without diabetes.

[1] https://www.actuaries.org.uk/learn-and-develop/research-and-knowledge/actuarial-research-centre-arc/current-research/analysis-diabetes-mortality-and-morbidity-risk for further information.

[2] DWP conducted three surveys for companies based in the UK and Ireland, Mainland China and the rest of Asia, due to logistical reasons. For participation in UK and Ireland, the majority are in the UK. The survey in Mainland China was translated into Chinese to encourage higher participation. For simplicity, this paper refers to "The UK", "Mainland China" and "the rest of Asia".

	The main cause of death is likely to be linked to cardiovascular disease. However, the cause-specific analysis finds that other causes of death are also attributed to diabetes. The key to reducing risk is optimal glycaemic control which is difficult to achieve for some.
Morbidity and type 1 diabetes	Increased morbidity is understood to be a risk factor in those with type 1 diabetes; known microvascular, macrovascular and neuropathic complications are directly linked to glycaemic control. While the longevity of those with type 1 diabetes has improved considerably over the past century, this population remain at increased risk of a reduced life expectancy compared to those without diabetes. Nevertheless, a subgroup of individuals with type 1 diabetes may survive into older age despite living with diabetes. Certain clinical and biochemical features can identify these people.
Morbidity and type 2 diabetes	People living with type 2 diabetes are at risk of several different complications because of inadequate glycaemic control. These are much the same as those seen in type 1 diabetes and include damage to blood vessels and nerves resulting in micro- and macro-vascular complications. As the prevalence of diabetes increases, so will this significant morbidity burden.
Prediabetes	Increases the risk for diabetes and other chronic diseases. Also associated with excess morbidity and mortality risk. HbA1c alone does not capture all of those with dysregulation – insulin sensitivity and fasting analysis appear to be better correlated. Also, it has been observed that changes in glucose regulation may take place up to 18 years in advance of any diagnosis.
COVID-19 infection in people with diabetes	It has been reported that people with diabetes and COVID-19 pneumonia are more severely affected than those without diabetes when evaluating organ damage, inflammatory factors or hypercoagulability, and are more likely to progress into a worse prognosis. In addition, new-onset diabetes in those previously at little to no risk is being observed in those who have had COVID-19

Actuaries working in product design should consider whether the products they offer provide people with diabetes with coverage that is commensurate with the increase in risk (where applicable) compared to that of the general population without diabetes and whether appropriate allowance has been made for treatments including technology that allow for control of risk through stabilising glycaemia.

2. Global underwriting survey

A summary of the key observations:

- Diabetes is an important consideration in the medical underwriting process.
- The majority of insurers rely on reinsurers guidelines for people with diabetes, however, some do use their own possibly based on reinsurers guidelines.

- The outcomes across different regions surveyed demonstrate wide availability for mortality products, with lower accessibility in relation to critical illness and disability income products, particularly for the UK.
- The number of participants asking a specific question of the applicant as to whether they have 'prediabetes' is considerably lower across all regions in the survey.
- For the key rating factors such as age, gender, and smoker status there are differences between the different regions:
    - Age is used by 100% of insurers/reinsurers in the UK but by a lower number in Mainland China and the rest of Asia. Age is a key risk factor particularly for type 2.
    - Gender is considered less in the UK compared to Mainland China and the rest of Asia which may be to do with EU gender-neutral considerations, despite guidance from the European Commission indicating its use would be acceptable in relation to the different health outcomes.
    - Smoker status is an important rating factor where the UK has a high proportion of usage in risk assessment compared to Mainland China and the rest of Asia.
    - Physical activity and diet are key risk factors but there is currently a low usage of physical activity and diet measurements across all regions. Mainland China has a higher proportion of insurers using physical activity compared to the UK and the rest of Asia.
    - Other rating factors used such as BMI, Blood pressure, Lipid levels and HbA1c are commonly used across all regions.

Actuaries and Underwriters do need to consider the latest available information that allows for medical advances in treatments and technology when considering an appropriate price for life and morbidity products for people with diabetes. Is there a sufficient long-term evidence base or is it still too early for the industry to start making use of factors that demonstrate good control of glycaemia such as lifestyle factors and technologies that monitor blood glucose levels? Is it appropriate that access to critical illness and disability in the UK is severely limited?

4 Introduction

The last decade has seen significant advances in treatments for type 2 diabetes. Yet, the long-term impact of these advances is not yet fully appreciated. Currently, available risk estimates are derived from data that is over ten years old. However, it is important that the insurance industry ensures that the information they are using is up to date so they can price appropriately for people with diabetes.

The overarching aim of this research project is to develop a deeper understanding of the risks associated with a diagnosis of type 1 or type 2 diabetes, and the impact of recent improved treatments. More specifically our objectives are to:

1. understand the increased risk of medical complications, including the impact of behavioural and modifiable risk factors and implications for chronic conditions later in life
2. understand the information available to insurance underwriters and how this is used to underwrite this risk
3. gain insights from data by considering advanced data analytic techniques to understand relative risk factors
4. produce mortality tables at a granular level for lives with and without diabetes (inclusive of all age ranges)
5. produce morbidity tables at a granular level for incidence of diabetes.

This paper aims to present information on an extensive literature review and a global underwriting survey undertaken to understand how the industry, across different regions of the world, underwrites

people with diabetes or at risk of developing diabetes (objectives 1 and 2). More specifically we want to understand the information available to life insurance/reinsurance and how this is used to underwrite this risk.

The project commissioned by the Actuarial Research Centre (ARC), Pacific Life Re, Partner Re, Swiss Re, Legal & General and Zurich Insurance Group in partnership work with the University of Leicester University is focused on the last three objectives (3 to 5). This work will be covered in a separate publication.

This research will be of interest to those insurers/reinsurers that write protection business and longevity products. It will also be of interest from a public interest perspective in terms of how underwriters currently assess the risk of individual people with diabetes across different territories.

The working party wishes to thank all the companies and individuals that participated in the survey in which we achieved a global reach covering the UK, Mainland China and the rest of Asia. We also had good coverage of each market and the level of response was high (Table 2).

Table 2: Table of Regions, Countries and participating firms

Regions	Countries	Responses	Participating firms (if provided)
Europe	UK and Ireland	20	Just Group, LV, Pacific Life Re, Aegon, Scottish Widows, Vitality Life, New Ireland Assurance, Royal London Intermediary, Partner Re, Royal London Ireland, Aviva, Hannover Re, L&G, RGA, Old Mutual Wealth, Munich Re
The rest of Asia (ex-Mainland China)	Malaysia, Vietnam, Singapore, Indonesia	27	Swiss Re, AmGeneral Insurance Berhad, FWD Vietnam, Prudential Singapore, Great Eastern Takaful, Munich Re Retakaful, Great Eastern Life Malaysia, Berjaya Sompo Insurance Berhad, Allianz General Insurance Malaysia, MSIG Insurance (Singapore) Pte Ltd, Singlife, Sun Life Financial Indonesia, Bao Viet Life, FWD Singapore, RGA, Pacific Life Re, Prudential Assurance Malaysia Berhad
China	Mainland China, Hong Kong	55	Ping An, China Life, Sunshine Life, Tai Ping Life, PICC Health, AXA, Leapstack (Tech), Swiss Re, Shang Hai Life, King Dragon Life, Three Gorges Life, Bo Hai Life, New China Life, SCOR Re, Tai Kang Life, Guy Carpenter Re, Sun Life Everbright, Generali China Life, Guo Fu Life, Evergrand Life, Cigna & CMB Life, PICC Life, Happy Life, Ai Xin Life, Aegon THTF Life

Source: IFoA Global Underwriting Survey

The importance of understanding diabetes will have a broader societal aim. We hope this paper and the commissioned work with the University of Leicester can significantly contribute to and form a basis of discussion for insurers. More specifically:

- To widen life insurance coverage of customers with diabetes (type 1 and type 2). This work aims to potentially provide new insights to inform and provide evidence that may enable new approaches into how the industry underwrite people with diabetes. It includes protection and

longevity products (e.g., term, critical illness, income protection, other disability products and impaired annuities).

- Provide an up-to-date evidence base that better reflects more recent mortality improvements in diabetes treatment which may enable broader coverage for those diagnosed with diabetes.
- Improve underwriting transparency for people with diabetes (type 1 and type 2)
- Through wider dissemination and collaboration with diabetes organisations, to promote behavioural change to postpone or prevent chronic conditions emanating from diabetic conditions through good management and lifestyle changes.
- To contribute to a discussion for insurers/reinsurers to inform debate and to encourage innovation around how the industry can play a part in supporting people with diabetes or preventing diabetes.

5 Literature review

5.1 Diabetes and mortality

5.1.1 Introduction

Diabetes Mellitus is a disease caused by a lack of insulin (type 1) or an increased resistance of the body to insulin (type 2) and is characterised by high blood glucose levels. The resulting chronic high blood glucose levels (hyperglycaemia) are associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.

This literature review has been undertaken by the IFoA working party on diabetes and represents the currently accessible and freely available published literature on mortality risk associated with type 1 diabetes and type 2 diabetes.

5.1.2 Main Types

5.1.2.1 Type 1 diabetes

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease caused by the pathogenic action of T lymphocytes on insulin-producing beta-cells in the pancreas. It is lethal unless treated with exogenous insulin.

5.1.2.2 Type 2 diabetes (T2DM)

T2DM, as previously highlighted, is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion which in some cases becomes absolute. Insulin resistance is usually well established by the time of diagnosis, and hyperglycaemia escalates as beta-cell function deteriorates.

5.1.3 Complications

People with diabetes also run a greater risk of developing one or more severe health complications, which can greatly impact their independence and quality of life as well as reduced life expectancy.

Once a patient has developed diabetes, the major aim of clinical care is to prevent complications and morbidity related to the disease. The most common complication of diabetes is cardiovascular disease manifested as coronary artery disease, peripheral vascular disease or carotid artery and other cerebrovascular diseases.

In the UK, diabetes is the leading cause of blindness in working-aged people, and the main contributor to kidney failure, amputations and is one of the key contributors to cardiovascular disease, including heart attack and stroke.

5.1.4 Prevalence

The prevalence of diabetes in 2010 were estimated 3.1m or 7.4% of people aged 16 years and older in England which includes and type 1/type 2 and diagnosed/undiagnosed. Prevalence increases with age and is higher in men (8.6%) than in women (6.3%) although these rates vary around the UK. The APHO (Association of Public Health Observatories) Diabetes Prevalence Model (Holman et al., 2011) provides estimates of total diabetes prevalence for adults in England. The estimates are adjusted for age, sex, ethnic group and deprivation. Estimates are provided up to 2030 based on projected population change and projected increases in obesity. As with all modelled data, there is a degree of uncertainty around the APHO Diabetes Prevalence Model estimates. Uncertainty ranges have been calculated that give a plausible range in which the true value is likely to lie.

Between 2010 and 2030 the prevalence of diabetes among people aged 16 years and older is estimated to increase to 4.6m or 9.5%, a 28.3% rise over the period 2010 to 2030. Approximately half of this increase is due to the changing age and ethnic group structure of the population and about half is due to the projected increase in obesity. The prevalence of diabetes is not estimated to increase uniformly across England with some Primary Care Trusts (PCTs) projected to see the prevalence of diabetes almost double between 2010 and 2030. Eight of the ten PCTs that are estimated to experience the greatest proportional increase are in London.

The APHO model is not able to breakdown the prevalence between type 1 and type 2, where approximately 90% of prevalence is type 2. The method used to project future prevalence is based on the direct relationship between prevalence of overweight and obesity which is more evident for type 2 rather than type 1 diabetes. As a result, the APHO model may slightly overestimate prevalence, however, there is evidence of increasing prevalence of type 1 diabetes as well, so overall impact on the validity of the projected prevalence is not likely to be material.

5.1.5 Standards of Care

Patients with diabetes in England and Wales are supposed to receive a planned programme of nationally recommended checks each year. This forms part of personalised care planning that enables them and their healthcare professionals to jointly agree on actions for managing their diabetes and meeting their individual needs. Derived from both the National Service Framework (NSF) (Department of health, n.d.) and NICE guidance (NICE, n.d.-a) on diabetes. There are 9 Key Care Processes which are outlined below:

Table 3: National Service Framework (NSF) and NICE guidance on diabetes there are 9 Key Care Processes

Blood glucose level measurement	HbA_{1c} [3]optimum level 6.5%
Blood pressure measurement	<140/80mmHg with no kidney, eye or cerebrovascular damage, <130/80mmHg with evidence of kidney, eye or CV damage
Cholesterol level measurement	TC <4.0mmol/l; LDL-C <2.0 mmol/l
Retinal screening	Annual screening
Foot and leg check	Annual screening
Kidney function testing (urine)	Urinary albumin <2.5mg/mmol for men; <3.5mg/mmol women
Kidney function testing (blood)	Serum creatinine >150 micromol/L - discontinue metformin
Weight check	Aim for a BMI of 18.5-24.9
Smoking status check	check smoking status at annual review and smokers should be referred to local smoking cessation service

To provide a comprehensive view of diabetes care in England and Wales, the NHS conducts an annual audit, the National Diabetes Audit (NDA), which measures the effectiveness of diabetes healthcare against NICE Clinical Guidelines and NICE Quality Standards. The audit also captures complication rates and mortality which are published separately, the latest at time of writing of which was published in 2019.

[3] Glycated haemoglobin or glycosylated haemoglobin (haemoglobin A1c, HbA1c, A1C, or Hb1c; sometimes also HbA1c) is a form of haemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. In diabetes mellitus, higher amounts of glycated haemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, and retinopathy. Monitoring HbA1c in diabetic patients may improve outcomes.

Here we report the NDA release relating to associated mortality published in 2019 which reported on data from the 2015-2016 Audit; National Diabetes Audit 2017-2018 Report 2a Complications and Mortality (complications of diabetes) (NDA HQIP, 2019b)

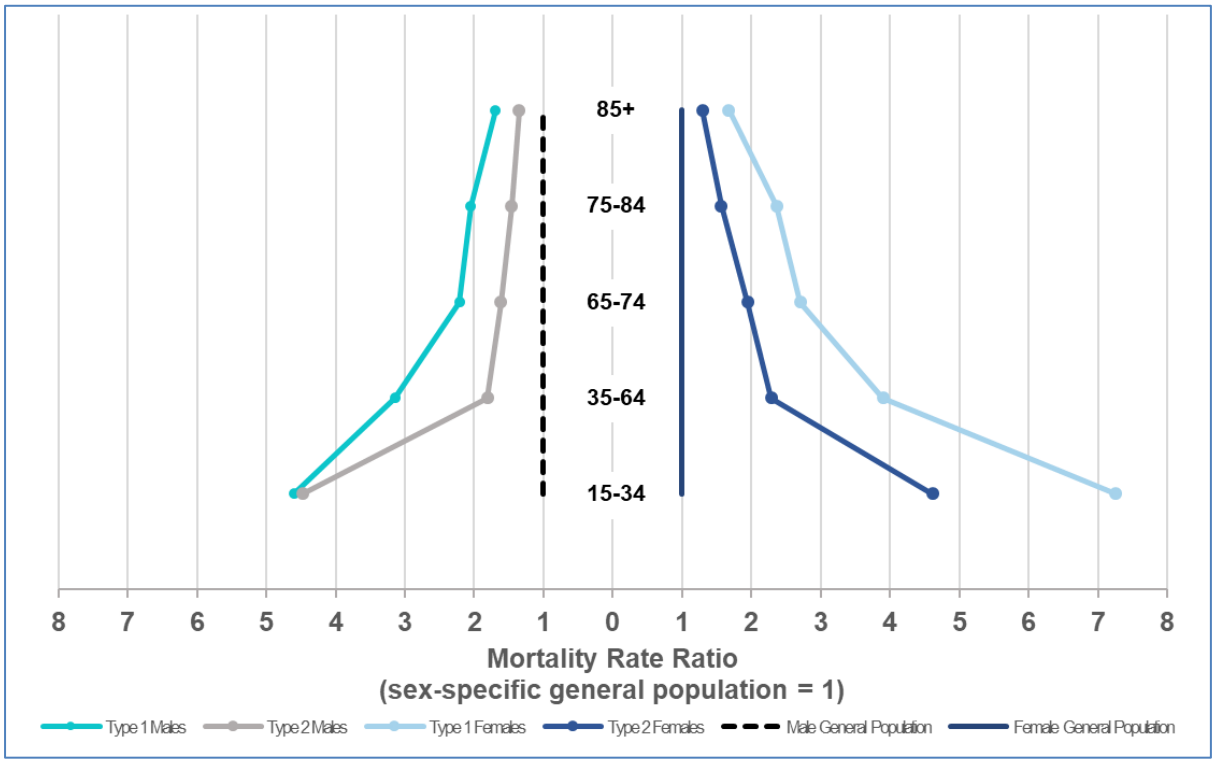
Table 4, Figure 1, Table 5).

Table 4: displays a summary of the findings relating to type 1 and type 2 diabetes.

		SMR	**Additional risk of death**
Males	Type 1	240	140.5%
	Type 2	149	49.1%
Females	Type 1	259	159.2%
	Type 2	152	51.7%
Males & Females	Type 1	248	148%
	Type 2	150	50.2%

Table 4. Standardised mortality rates (SMR) in type 1 and type 2 diabetes, England and Wales

Figure 1: Age specific mortality rate ratios by type of diabetes and sex, 2015-16 audit, England and Wales, deaths in 2017



The relative risk of death is increased at all ages, in both men and women, in younger people more than older people, and greater risk was observed in those with type 1 diabetes.

The proportion of deaths due to vascular outcomes is higher than cancer outcomes in the diabetic population. In the non-diabetic population, they are broadly similar (Table 5).

Table 5: displays the causes of death for all diabetic types combined

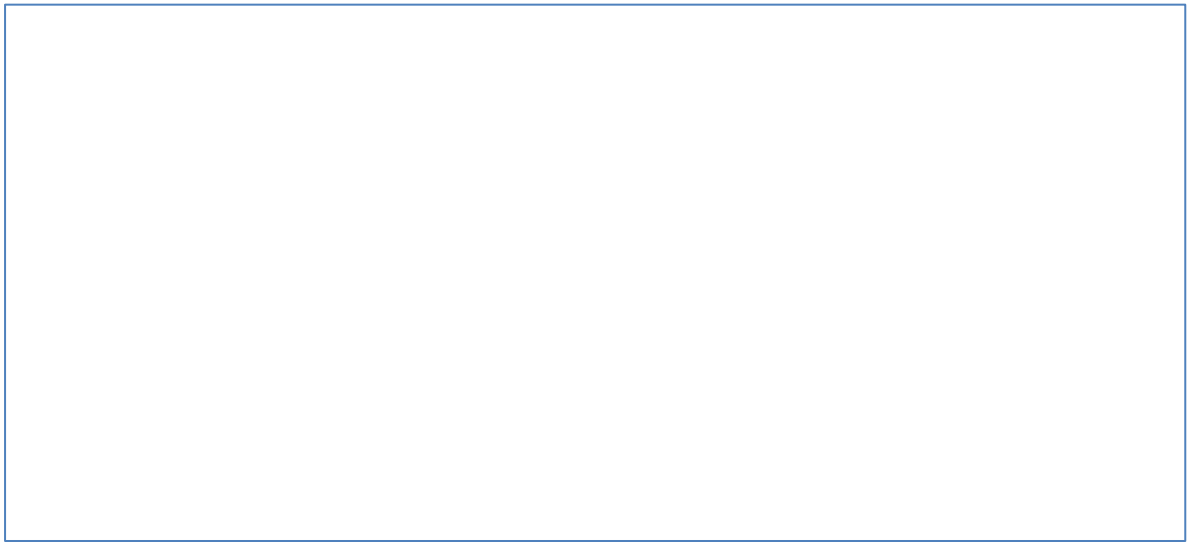
Death	**Diabetic**	**Non-Diabetic**
Cancer	25.2%	28.3%
Vascular	32.1%	27.8%
Neither Cancer or vascular	41.3%	41.5%
Unknown	1.3%	2.4%

Table 5. Causes of death in diabetic and non-diabetic subjects, England and Wales

The NDA also provides analysis for mortality in relation to care process completion (NDA HQIP, 2018). Two cohorts of people with diabetes, aged 20 years and over and alive as of 31st March 2013 were chosen to evaluate how full care process completion (all 21 checks, 'Complete') and significantly reduced care process completion (12 checks or less, 'Incomplete') are associated with the outcomes of people with diabetes. Only three care processes, measurement of HbA1c, blood pressure and serum cholesterol, were included in the analysis.

For all age groups, the death rate during the follow-up period was higher for the group whose care process completion during the preceding seven years was incomplete – twice as high for most age groups. Figure 2 displays the percentage of people with Type 1 diabetes who died during the follow-up period by age.

Figure 2: Percentage of people with Type 1 diabetes who died during the follow-up period, by age



This clearly demonstrates the increased mortality for those not able to achieve optimal care processes. A similar picture emerges for those with type 2 diabetes in Figure 3**.**

Figure 3: Percentage of people with Type 2 and other diabetes who died during the follow-up period, by age

In addition, the latest publication on care processes covers the period up to 2021 and therefore provides an insight into how the pandemic affected management of diabetes.

In summary:

- During the COVID 19 pandemic, care process completion declined everywhere but there was greater geographical variation than usual. The greatest impacts were on foot examination, weight measurement, and retinal screening. Least affected were blood tests and blood pressure. Most affected were BMI checks, retinal screening and foot examination. The long-term low rates of urine albumin checks remain lowest.
- During the COVID 19 pandemic, glucose control improved in people with type 1 diabetes but deteriorated in those with type 2 and other types of diabetes; blood pressure deteriorated in all; and use of statins was relatively unchanged.
- Blood pressure treatment target achievement is on a long-term downward trend, but HbA1c shows steady improvement. In England, but not in Wales, there has been an increase in the percentage of people with type 1 diabetes achieving all 3 treatment targets since the new statin treatment-based definition was introduced in 2017-18.

The NDA provides an excellent insight into the outcomes for people with diabetes in England and Wales and that achieving optimal care processes is key to improved mortality.

5.1.6 Mortality

It is generally accepted that there is excess mortality risk associated with a diagnosis of diabetes and this varies according to several factors. Studies that have estimated all-cause mortality risk and survival with diabetes are set out below.

5.1.6.1 Type 1 Diabetes

A meta-analysis published in 2014 sought to review published studies on the risk ratio (RR) of mortality of Type 1 diabetes patients compared to the general population, and to examine the temporal changes in the RR of mortality over time. (Lung et al., 2014)

26 studies with a total of 88 subpopulations were included in the meta-analysis. Results of the overall meta-analysis of 88 observations are shown in Table 6. The overall RR of mortality was 3.82 (95% CI 3.41, 4.29) compared to the general population.

Table 6: Meta-analysis results by different categories, showing the number of observations used, the pooled estimate and 95% confidence intervals

	No. of studies	Pooled estimate (95% CI)
All studies	88	3.82 (3.41–4.29)
Studies commenced before 1970	10	5.80 (4.20–8.01)
Studies commenced between 1971–1980	12	5.06 (3.44–7.45)
Studies commenced between 1981–1990	50	3.59 (3.15–4.09)
Studies commenced after 1990	16	3.11 (2.47–3.91)
Studies with patients age at diagnosis before 18 years	41	4.93 (4.13–5.88)
Studies with patients age at diagnosis after 18 years	8	2.41 (1.75–3.32)
Male	44	3.25 (2.82–3.73)
Female	44	4.54 (3.79–5.45)
United Kingdom studies	28	3.78 (3.13–4.57)
European studies	66	3.56 (3.16–4.00)
Non-European studies	22	4.63 (3.28–6.55)

This study has estimated that people with type 1 diabetes have an elevated risk of mortality when compared to the general population, although the gap between the two populations has been decreasing. However, the sub-group meta-analyses suggests that the largest reductions in relative mortality have been achieved prior to 1980.

Livingstone et al (Livingstone et al., 2015) set out to examine the current life expectancy in people with and without type 1 diabetes in Scotland. Also, this study examined whether any loss of life expectancy in patients with type 1 diabetes is confined to those who develop kidney disease. They found that estimated life expectancy for patients with type 1 diabetes in Scotland based on data from 2008 through 2010 indicated an estimated loss of life expectancy at age 20 years of approximately 11 years for men and 13 years for women compared with the general population without type 1 diabetes.

Whilst this confirms the excess mortality in type 1 diabetes, the good news is that life expectancy has improved in some populations with diabetes over time. The Pittsburgh Epidemiology of Diabetes Complications (EDC) study (Miller et al., 2012) is a long-term cohort study which examined mortality and life-expectancy changes over time in a U.S. cohort with long-term (>30 years) follow-up in participants who were all diagnosed with childhood-onset type 1 diabetes between 1950 and 1980. For this analysis, researchers compared two sub-cohorts based on the year of diabetes diagnosis (1950–1964 [n=390] vs. 1965–1980 [n= 543]). This analysis reports that those diagnosed with childhood-onset type 1 diabetes in the late 1960s and 1970s experienced only a 4- to 6-year loss-of-life expectancy compared with >17 years for those diagnosed in the 1950s and early 1960s.

Rawshani et al (Aidin Rawshani et al., 2017) also report on mortality improvements; in Sweden from 1998 to 2014, mortality and the incidence of cardiovascular outcomes declined substantially among

persons with type 1 diabetes (~<40%). The changes observed in this study most likely reflect a combination of advances. (This study also reports ~<20% reduction in those with type 2 diabetes)

What drives the differences in mortality risk? A 2018 analysis (Araz Rawshani et al., 2018) aimed to examine how age at diagnosis of type 1 diabetes relates to excess mortality and cardiovascular risk. The study concluded that independently of diabetes duration, age at onset of type 1 diabetes appears to be an important determinant of survival and all cardiovascular outcomes.

Early-onset type 1 diabetes is associated with up to 30-times an increased risk of serious cardiovascular outcomes, with risk levels being 90 times higher for women with early-onset diabetes, who also die around 18 years earlier than their diabetes-free counterparts. Huxley et al (Huxley et al., 2015) also found that women with type 1 diabetes carry a greater excess mortality risk; women with type 1 diabetes were observed in meta-analysis to have a roughly 40% greater excess risk of all-cause mortality, and twice the excess risk of fatal and nonfatal vascular events, compared with men with type 1 diabetes.

Additionally, Collier et al (Collier et al., 2018) report that patients with type 1 diabetes had higher mortality rates than non-diabetic individuals (HR, 3.20; P < .01), with relative mortality in female individuals with type 1 diabetes being higher than that in males (OR, 2.38 vs 1.52; P < .01). Increasing age (HR, 2.37), smoking (HR, 1.85), IHD (HR, 1.62) and hypertension (HR, 1.21) (all P < .01) increased mortality risk.

5.1.6.2 Type 2 Diabetes

There are several registry and cohort-based studies around the world that specifically monitor the progress and outcome of diabetic populations. One such study is the Swedish Registry for Cause-Specific Mortality Analysis published in 2015 (Tancredi et al., 2015) which reported on the excess risks of death from any cause and death from cardiovascular causes among persons with type 2 diabetes and various levels of glycaemic control and renal complications. Overall, mortality among persons with type 2 diabetes, as compared with that in the general population, (adjusted hazard ratio, 1.15; 95% confidence interval [CI], 1.14 to 1.16), varied greatly, from substantial excess risks in large patient groups to lower risks of death depending on age, glycaemic control, and renal complications.

Holden et al (Holden et al., 2017) report that the prevalence of Type 2 diabetes in the UK trebled between 1991 and 2013; the incidence of new cases of Type 2 diabetes has somewhat plateaued since 2005. Estimated median survival increased from 14 years in 1991 to 22 years in 2009 and average HbA1c levels reduced from 8.6% in 1991 to 7.5% in 2013.

Glycaemic variability has been identified as a key driver in mortality in diabetes. Hirakawa et al. (Hirakawa et al., 2014) report that variability at each clinical visit (visit-to-visit variability – VVV), particularly increases in HbA1c, can be associated with an increased risk of vascular events and mortality. In this study, variability in HbA1c and in fasting glucose predicted future macrovascular and microvascular events and all-cause deaths independent of cardiovascular risk factors. Variability in fasting glucose and maximum fasting glucose were stronger predictors than HbA1c variability.

HbA1c variability has also been the subject of evaluation in a 2018 study (Orsi et al., 2018) reporting on various measures of haemoglobin (Hb) A1c variability, compared with average HbA1c, as independent predictors of mortality among patients with type 2 diabetes. This study provides compelling evidence that HbA1c variability is a strong and independent predictor of total mortality in patients with type 2 diabetes and is more powerful than average HbA1c.

Unadjusted Cox proportional hazards regression (Table 7) showed that mortality increased with the quartiles of HbA1c-MEAN, HbA1c-SD, HbA1c-CV and HbA1c-AdjSD; these relationships remained after adjusting for age and gender (model 1), but not for multiple confounders (model 2) in the case of HbA1c-MEAN.

Table 7: All-cause mortality by quartiles of HbA1C-MEAN and of measures of HbA1C variability

	Unadjusted			Adjusted Model 1			Model 2		
Variables	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
HbA1c-MEAN			<.0001			<.0001			
Quartile I	1.000	–	-	1.000	-	–			
Quartile II	1.116	0.979-1.273	.101	1.026	0.900-1.170	.700			
Quartile III	1.257	1.106-1.428	<.0001	1.171	1.030-1.332	.016			
Quartile IV	1.527	1.349-1.729	<.0001	1.493	1.318-1.690	<.0001			
HbA1c-SD			.001			<.0001			<.0001
Quartile I	1.000	–	-	1.000	–	–	1.000	–	–
Quartile II	1.185	1.039-1.352	.011	1.206	1.058-1.376	.005	1.124	0.985-1.284	.084
Quartile III	1.412	1.244-1.604	<.0001	1.490	1.312-1.693	<.0001	1.306	1.147-1.487	<.0001
Quartile IV	1.429	1.259-1.623	<.0001	1.779	1.566-2.021	<.0001	1.441	1.262-1.645	<.0001
HbA1c-CV			<.0001			<.0001			<.0001
Quartile I	1.000	–	-	1.000	–	–	1.000	–	–
Quartile II	1.118	0.981-1.275	094	1.196	1.050-1.364	.007	1.153	1.011-1.315	.033
Quartile III	1.397	1.233-1.584	<.0001	1.521	1.341-1.724	<.0001	1.354	1.192-1.537	<.0001
Quartile IV	1.321	1.163-1.499	<.0001	1.692	1.490-1.922	<.0001	1.452	1.274-1.654	<.0001
HbA1c-AdjSD			<.0001			<.0001			<.0001
Quartile I	1.000	–	–	1.000	–	–	1.000	–	–
Quartile II	1.191	1.044-1.359	.009	1.204	1.056-1.374	<.0001	1.127	0.987-1.287	.078
Quartile III	1.409	1.240-1.601	<.0001	1.475	1.298-1.676	<.0001	1.281	1.125-1.460	<.0001
Quartile IV	1.458	1.284-1.656	<.0001	1.787	1.573-2.031	<.0001	1.445	1.266-1.650	<.0001

Abbreviations: HbA1c, haemoglobin A1c,; HbA1c-MEAN, average HbA1c; HbA1c-SD, standard deviation of HbA1c; HbA1c-CV, coefficient of variation of HbA1c; HbA1c-AdjSD, adjusted SD of HbA1c; HR, hazard ratio; CI, confidence interval. Survival analysis by Cox proportional hazards regression according to quartiles of HbA1c-MEAN, HbA1c-SD, HbA1c-CV, and HbA1c-AdjSD, unadjusted or adjusted for age and gender (model 1) or multiple confounders (model 2).

A possible mechanism is that periods of high HbA1c levels may be "remembered" due to long-lasting epigenetic[4] changes, or that the effect mirrors poor compliance with medication, the presence of multiple co-morbidities that increase insulin resistance or poor quality of life and support.

Modern treatment regimens for people with type 2 diabetes offer greater control and hopefully reduced variability. In fact, incretin-based therapies (including GLP-1RAs and DPP-4 inhibitors) and Thiazolidinediones (TZDs) offer a higher probability of sustained lower HbA1c levels compared to Sulphonylureas (SUs), insulin or metformin. (Montvida et al., 2018)

Other factors associated with mortality and type 2 diabetes include age at diagnosis and duration. In one study, Huo et al (Huo et al., 2018) observed an increase in mortality rates for people with diabetes in an Australian population. Over a 15-year time frame, all-cause mortality rate ratios for people with diabetes increased with age and duration up to 1.2 for 5 years initial duration to 1.3 for 10 years initial duration. CVD mortality rate ratios ranged up to 1.6 for 10 years initial duration. This research team acknowledges that the higher mortality with duration may be due to the combination of early age at onset, and duration (the latter likely to lead to increased exposure to hyperglycaemia, which in turn is a component in the increased mortality risk).

A study that is now becoming outdated, but still worth including, is one that published tables that report the life expectancy associated with levels of major modifiable risk factors for patients with type 2 diabetes (Leal et al., 2009). For this analysis, the authors used forecasts from the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model which is a computer simulation model for forecasting the likely first occurrence of major diabetes-related complications and death in patients with diagnosed type 2 diabetes.

[4] Epigenetics is the study of how your behaviors and environment can cause changes that affect the way your genes work. Unlike genetic changes, epigenetic changes are reversible and do not change your DNA sequence, but they can change how your body reads a DNA sequence. (source: www.cdc.gov)

For illustrative purposes, the Outcomes Model was used to predict the life expectancy of patients with type 2 diabetes, 5 years after diagnosis, stratified into the following risk groups: age (55, 65, and 75 years old), sex (male, female), systolic blood pressure (120, 140, 160, and 180 mmHg), HbA1c (6, 8, and 10%), the ratio of total: HDL cholesterol (4–8), and smoking status (never smoked, current smoker).

Further, the study also reports the life expectancy of 65-year-old male and female patients at 1, 3, and 7 years after diagnosis. The modifiable risk factors were assumed to remain constant over time.

Table 8: Assessment of life expectancy in men and women with Type 2 diabetes. These men and women were assumed to have no previous diabetes-related complications, been diagnosed with the disease 5 years previously, and had a body mass index of 30 and 33 kg/m2, respectively.

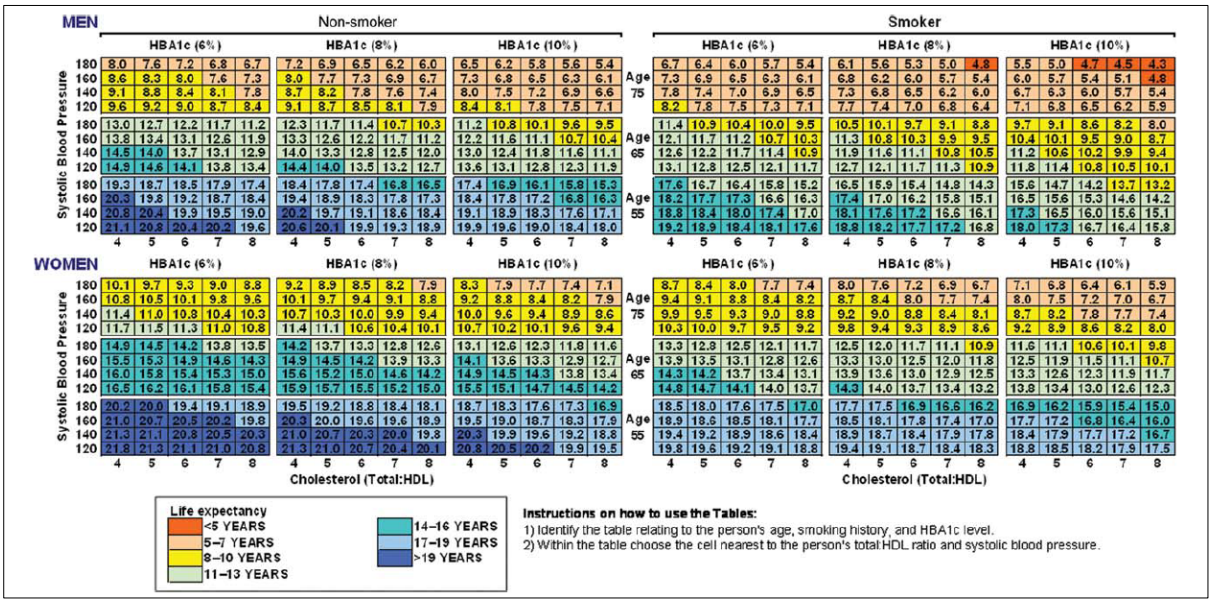
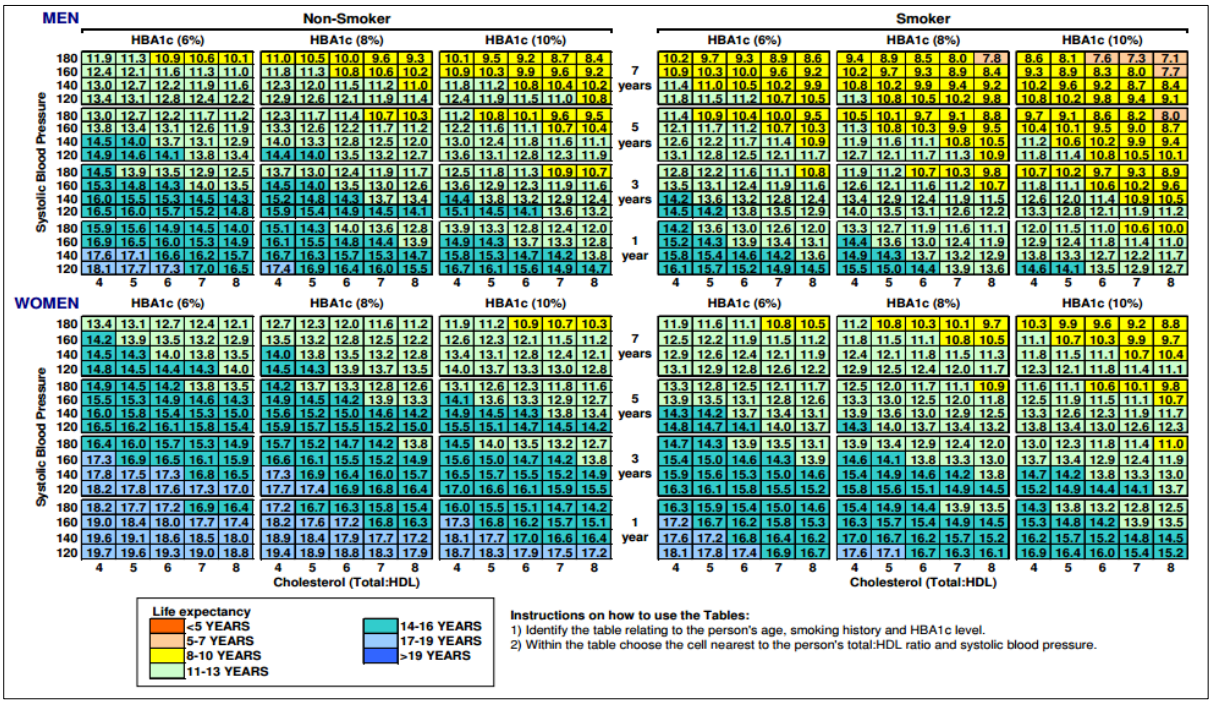


Table 8 demonstrates that there is a substantial gradient in survival across risk factors. For example, the estimated age-specific life expectancy of men with type 2 diabetes varies between 13.2 and 21.1 years at age 55 for patients in the highest to lowest risk groups.

In terms of duration of diabetes, life expectancy in years for men aged 65, for instance, in the highest to lowest risk groups varies between 10.0 and 18.1 at 1-year post-diagnosis, 8.9 and 16.5 at 3 years' post-diagnosis and 7.1 and 13.4 at 7 years' post-diagnosis (Table 9).

The authors conclude that the life expectancy tables presented here provide a ready means of conveying potentially useful prognostic information to people with type 2 diabetes. The variation in life expectancy suggests substantial scope for increasing longevity by improving modifiable risk factors.

Table 9: Life expectancy in men and women with type 2 diabetes aged 65 years at one, three, five and seven years after diagnosis. These men and women were assumed to have no previous diabetes-related complications and a body mass index of 30 and 33 kg/m2, respectively.



5.1.6.3 All-cause mortality in diabetes

Most of the studies that have analysed the rates of increased mortality in people with diabetes have provided data on all-cause mortality. Overall, this is probably because cardiovascular disease is the leading cause of death in people with diabetes. Cause-specific mortality analysis data from the Cancer Prevention Study-II[5] provide some insights into the wider causes of death. (Campbell et al., 2012)

26 years of follow-up of over 1 million US adults found that diabetes was associated with not only cardiovascular mortality but also cancers of the liver, pancreas, endometrium, colon, oral cavity, bladder and breast. In addition, diabetes was also associated with increased mortality for infectious diseases, accidental death, suicide, skin diseases, cirrhosis of the liver, pulmonary diseases, and other non-cancer causes as set out in Figure 4 and Figure 5.

[5] The Cancer Prevention Study II (CPS-II), which began in 1982, is a prospective mortality study of approximately 1.2 million American men and women.

Figure 4: RRs (95% CI) for deaths from noncancer outcomes comparing female (A) participants with diabetes (DM) with female participants without diabetes (No DM) at baseline, adjusting for age, education, BMI, smoking, alcohol intake, vegetable intake, red meat intake, physical activity, and aspirin use, in the CPS-II, 1982–2008.

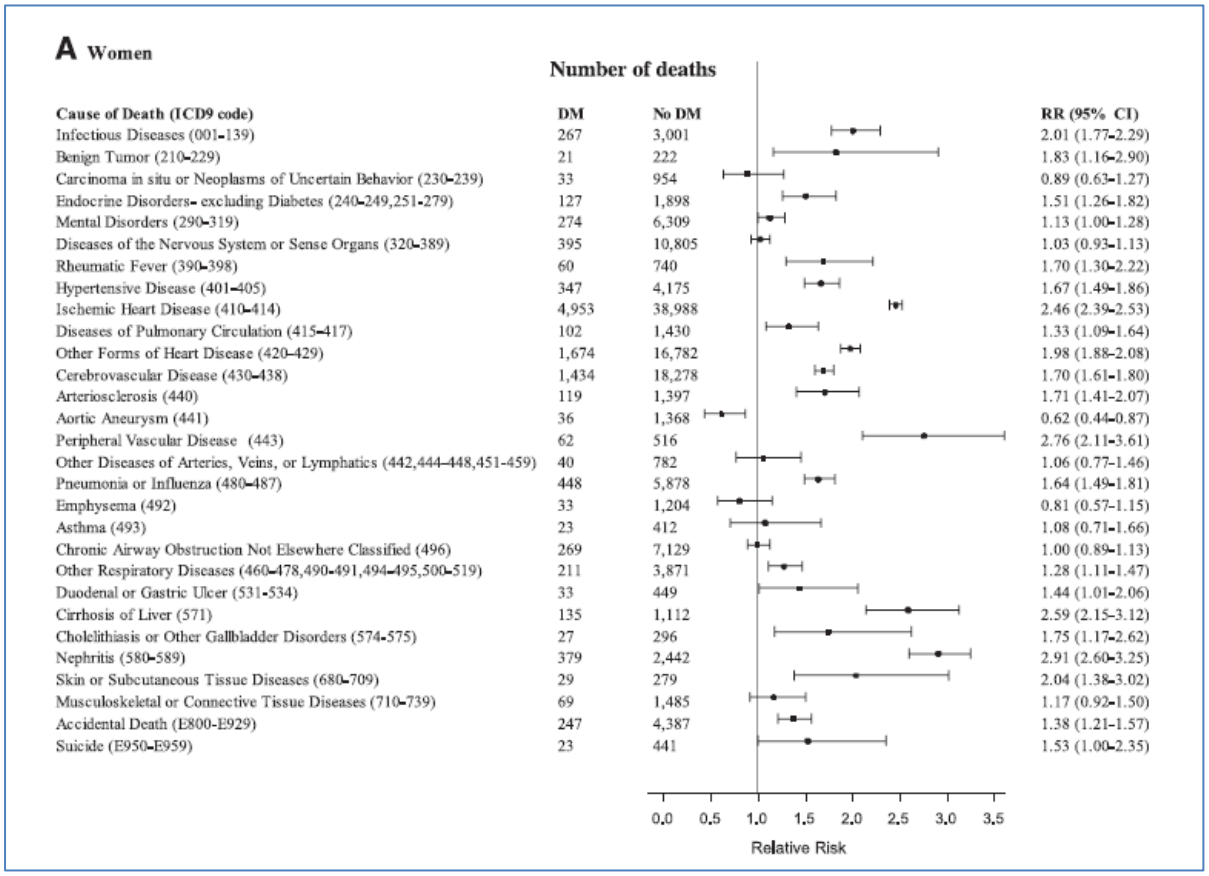


Figure 4 shows a significant higher risk of death for female lives due to certain causes such as peripheral vascular disease, cirrhosis of the liver and nephritis. Generally, across the range of causes due to heart disease there is a significant relative risk factor. However, the relative risk factor is great than 1 for a range of other causes of death as well including infectious diseases and flu. Aortic Aneurysm is the only cause that is significantly below 1.

Figure 5: RRs (95% CI) for deaths from noncancer outcomes comparing male (B) participants with diabetes (DM) with male participants without diabetes (No DM) at baseline, adjusting for age, education, BMI, smoking, alcohol intake, vegetable intake, red meat intake, physical activity, and aspirin use, in the CPS-II, 1982–2008.

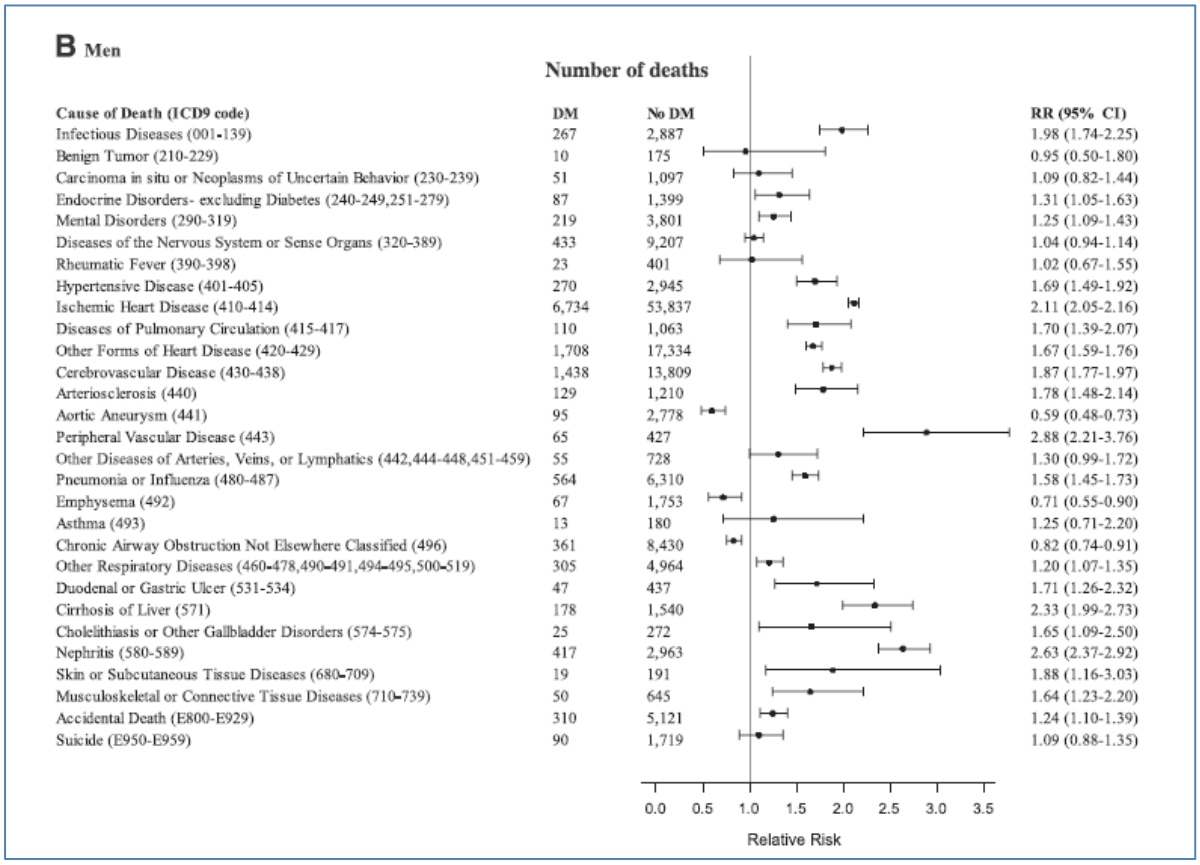


Figure 5 for male lives is a similar pattern to female lives for conditions where the relative risk factor is significantly above 1. This time there are three conditions below 1 (Aortic Aneurysm, Emphysema, Chronic Airway Obstructive Not Elsewhere Classified).

This type of analysis provides useful insights for underwriters and actuaries to understand the drivers in the all-cause mortality experience. At outset underwriters would consider any co-morbidities present as this would give an indication as how well the person with diabetes controls their condition and it will also give an indication as to how long they have had diabetes. It also provides insights into potential co-morbidities a person with diabetes is more likely to develop prior to death.

Medical information on the customer/applicants may be available to the underwriter/actuary at underwriting stage on customers with diabetes with co-morbidities. It is also possible if underwriting is continuous to collect some information from the customer over time, on modifiable risk factors. For in-force life business there will be little if any information available on customers health or prevalence of co-morbidities.

However, this study is dated so it is important that the industry refers to more up-to-date analysis that allows for changes in medical treatment and technologic changes in monitoring glycaemic control over time. The study also doesn't provide details of factors around how well a person with diabetes controls their glucose levels over time and other lifestyle factors that could reduce their mortality risk. The industry should consider other factors to understand the risk at a more granular level and capture information on how well somebody with diabetes controls their blood sugar.

5.1.7 Conclusion

Those with diabetes are at increased risk of morbidity and excess mortality compared to the general population without diabetes. Whilst it is generally understood that the main cause of death is likely to be linked to cardiovascular disease, cause-specific mortality analysis finds that other causes of death are recorded in those with diabetes.

The key to reducing risk is optimal glycaemic control which for some is difficult to achieve as is evidenced by data from the National Diabetes Audit.

However, the currently available published analysis does not capture the impact of modern treatments in type 1 and type 2 diabetes, and therefore, this literature review is unable to reflect the current picture of diabetes and mortality risk.

It important the industry can access contemporary data on the relative risks, lifestyle factors and other drivers known to impact optimal diabetes control. ,

5.1.8 Recommendation

Actuaries working in product design and Underwriters should consider whether the products they offer provide people with diabetes have coverage that is commensurate with the increase in risk (where applicable) compared to that of the general population without diabetes and whether appropriate allowance has been made for treatments that allow people with diabetes to control risk through monitoring glycaemia.

In summary, the implications for actuaries and underwriters are to incorporate the key insights of these studies into how they underwrite or price people with diabetes:

- Type 1 and type 2 should be considered separately.
- Glycaemic variability has important implications for the relative risk (diabetes vs non-diabetes). HbA1c variability is a more powerful predictor than average HbA1c.
- Allowing for technological advances that improves monitoring of glucose levels in the blood and enables better glycaemic control
- Allowing for medical advances, such as incretion-based therapies and Thiazolidinediones, that improve glycaemic control and therefore reduce mortality risk.
- Age at diagnosis and duration since diagnosis are also important factors for mortality risk.
- Allowing for modifiable risk factors such as cholesterol, systolic blood pressure, smoking habit and HbA1c level
- Understanding mortality by cause shows diabetes has a much wider impact than cardiovascular disease and includes increased risk for some cancers and infectious diseases.

We consider in more detail the underwriting factors currently used in section 6.

5.2 Diabetes and morbidity – Type 1

5.2.1 Risk factors

Increased morbidity is understood to be a risk factor in those with type 1 diabetes: known microvascular; macrovascular; and neuropathic complications that are directly linked to glycaemic control. For example, Timar and Albai (Timar & Albai, 2013) report that the percentage of chronic microvascular complications of diabetes is increasing together with HbA1c, being significantly higher (about three times) in patients with values above 7%.

White et al (White et al., 2017) set out to determine the relationship between glycaemic control trajectory and the long-term risk of severe complications in people with type 1 diabetes mellitus, as well as the effects of paediatric and adult HbA1c levels.

This is a data linkage study of data for adults with childhood-onset type 1 diabetes (diagnosed during 1975 -2010) who had transitioned from paediatric diabetes care at the Royal Children's Hospital (Melbourne) to adult diabetes care at the Royal Melbourne Hospital during 1992 - 2013.

Severe complications were categorised as severe diabetic retinopathy (SDR), chronic kidney disease, ulceration or amputation, and death. Mean HbA1c levels were calculated for the paediatric and adult periods. Four glycaemic control trajectories were defined according to mean paediatric and adult HbA1c levels:

- Stable low (paediatric and adult HbA1c < 66 mmol/mol)
- Improving (paediatric HbA1c > 66 mmol/mol, adult HbA1c < 66 mmol/mol)
- Worsening (paediatric HbA1c < 66 mmol/mol, adult HbA1c > 66 mmol/mol) and
- Stable high (paediatric and adult HbA1c > 66 mmol/mol).

503 eligible participants (253 men) were identified, 26 (5.2%) of whom had at least one severe complication, including 16 with SDR (3.2%). No-one in the stable low group, but 4% of the improving, 1% of the worsening, and 7% of the stable high groups developed SDR.

Higher mean paediatric (per 10.9 mmol/mol increase: odds ratio [OR], 2.9; 95% CI, 1.9 - 4.3; P < 0.01) or adult HbA1c levels (OR, 2.1; 95% CI, 1.4 - 3.1; P < 0.01) were associated with increased risk of SDR, as was longer duration of type 1 diabetes (per additional year: OR, 1.3; 95% CI, 1.2 - 1.5; P < 0.01). (Table 10)

SDR was associated with higher paediatric HbA1c levels, independent of glycaemic control during adulthood. It was not documented in patients with a stable low glycaemic control trajectory. Target-based treatment from the time of diagnosis of type 1 diabetes in childhood is required to reduce the risk of SDR during adulthood.

Table 10: Associations of mean HbA1c, and HbA1c variability (standard deviation) in paediatric and adult settings with odds of retinopathy in adulthood

	Severe retinopathy								
	Model 1			Model 2			Model 3		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Mean HbA_{1c} in childhood, 10.9 mmol/mol	2.4	1.5-4.0	0.001	-	-	-	3.2	1.5-7.5	0.004
Mean HbA_{1c} in adulthood, 10.9 mmol/mol	-	-	-	1.6	0.9-2.6	0.09	2.6	1.2-5.8	0.02
Paediatric HbA_{1c} standard deviation CoV	0.5	0.1-1.9	0.3	-	-	-	0.2	0.03-1.2	0.08
Adult HbA_{1c} standard deviation CoV	-	-	-	3.3	1.0-1.8	0.04	1.8	0.5-6.3	0.4
Duration of type 1 diabetes, years	1.2	1.0-1.4	0.01	1.4	1.1-1.8	0.003	1.4	1.1-1.9	0.01
Female sex	1.1	0.2-5.3	0.9	0.9	0.2-4.9	1.0	0.4	0.05-2.8	0.3
Age at diagnosis, years	1.2	0.9-1.5	0.1	1.3	0.9-1.8	0.06	1.3	0.9-1.7	0.2
Age at transition, years	0.9	0.5-1.8	0.8	0.9	0.4-2.0	0.04	0.1	0.4-2.7	0.97

Abbreviations: OR, odds ratio; CI, confidence interval

Clinical treatment goals for type 1 diabetes mellitus (T1DM) have changed since the Diabetes Control and Complications Trial (DCCT) demonstrated reduced long-term complications with intensive diabetes therapy. There have been few longitudinal studies to describe the clinical course of T1DM in the age of intensive therapy.

Whilst a little dated now, Nathan et al (Nathan et al., 2009) describe the then current-day clinical course of T1DM. This is a follow-up study of a cohort from the DCCT study from 1983-89.

In 1994, after completion of the DCCT, 1375 subjects (96% of the surviving cohort; 688 from the conventional arm and 687 from the intensive arm) agreed to participate in the EDIC follow-up study, which included annual examinations measuring diabetic complications. With the initiation of EDIC, the conventional treatment participants were offered instruction in intensive therapy reflecting the current recommendations for the management of TIDM. Long-term complications were tested for.

After 30 years of diabetes, the cumulative incidences of proliferative retinopathy, nephropathy, and cardiovascular disease were 50%, 25%, and 14%, respectively, in the DCCT conventional treatment group, and 47%, 17%, and 14%, respectively, in the EDC cohort. (Figure 6) The DCCT intensive therapy group had substantially lower cumulative incidences (21%, 9%, and 9%) and fewer than 1% became blind, required kidney replacement, or had an amputation because of diabetes during that time.

The frequencies of serious complications in patients with T1DM, especially when treated intensively, are lower than that reported historically. Overall, the prospects for patients with T1DM are far better than they were in the past.

Figure 6: Estimated cumulative incidences of proliferative retinopathy or worse (A), nephropathy (B), and cardiovascular disease (C) over time.

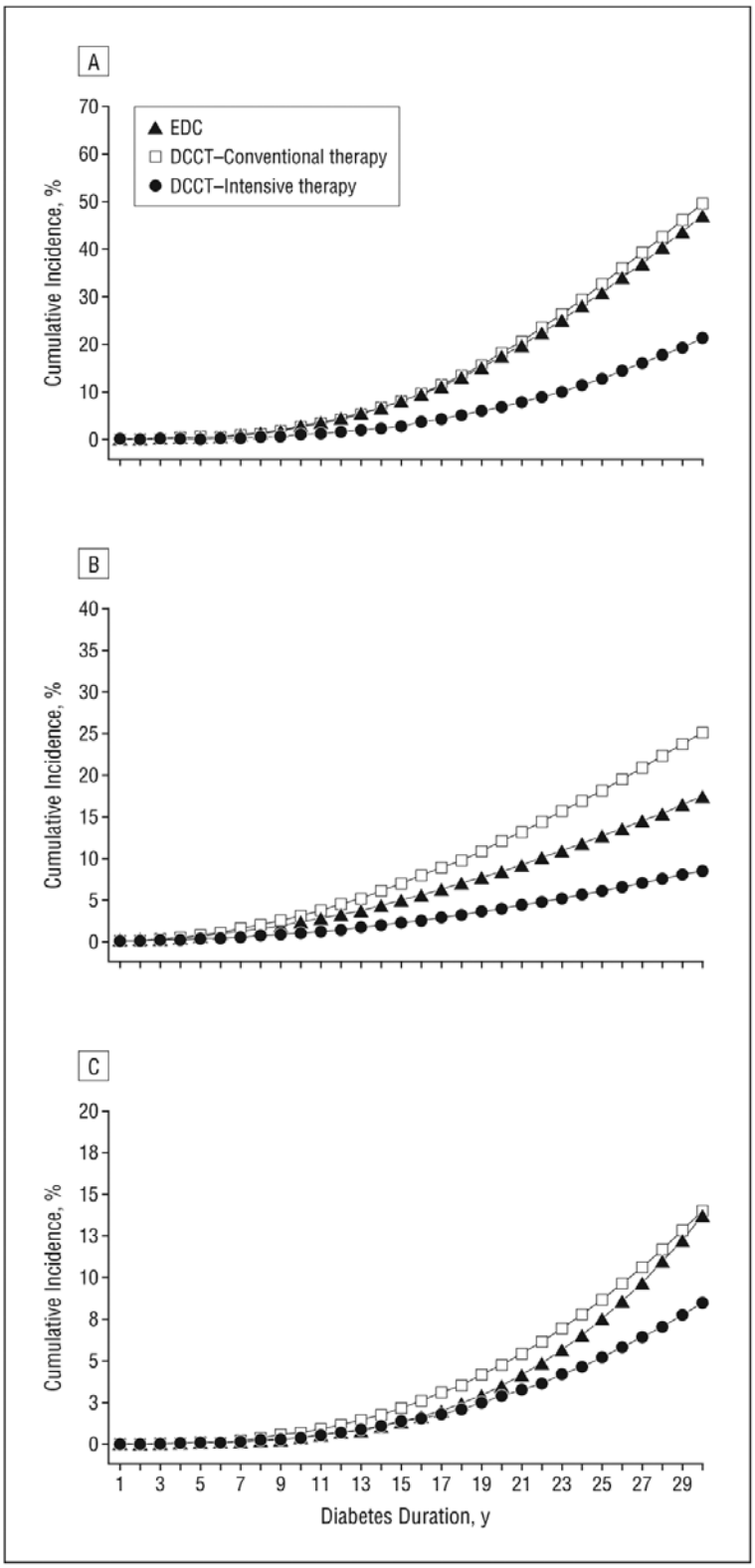


Figure 6.

Estimated cumulative incidences of proliferative retinopathy or worse (A), nephropathy (B), and cardiovascular disease (C) over time.

Nephropathy was defined as an albumin excretion rate of 300 mg/24 h or higher, a serum creatinine level of 2 mg/dL or higher, or dialysis or renal transplant

As we have previously observed, type 1 diabetes is associated with a higher risk of major vascular complications and death. A reliable method that predicts these outcomes early in the disease process would be helpful in risk classification. Published in 2015, Sabita et al (Soedamah-muthu et al., 2015) developed such a prognostic model and quantified its performance independently.

The following (easily obtainable) factors were considered by the model:

- Age
- HbA1c level
- Waist-hip ratio
- Albumin / creatinine ratio
- HDL cholesterol level

Other known prognostic factors, such as blood pressure, use of antihypertensive medication, LDL and smoking were not included in the model because of weak additional effects.

Kaplan Meier plots of hazard rates were produced for each cohort and the observed frequencies were plotted on them. With some recalibration of the graph intercept, the model was a reasonable predictor of the event hazard. EURODIAB data was used to develop the model. The development cohort included participants from 16 European countries. The model was then validated against three other cohorts.

Data from 1,973 participants with type 1 diabetes were analysed, and they were followed for seven years in the EURODIAB Prospective Complications Study. Strong prognostic factors of major outcomes were combined in a Weibull regression model (Figure 7 and Figure 8).

Prognostic factors identified were age, glycated haemoglobin, waist-hip ratio, albumin/creatinine ratio, and HDL cholesterol. A high-risk group could be identified with 15% risk after 3-years of follow-up, 24% after 5-years and 32% after 7-years.

The study has several limitations. Relatively low numbers of participants had major outcomes, as most participants were young.

Figure 7: Shows the Score chart developed in the EURODIAB Prospective Complications Study, to predict 3, 5 and 7 years of absolute risk of major outcomes in type 1 diabetes.

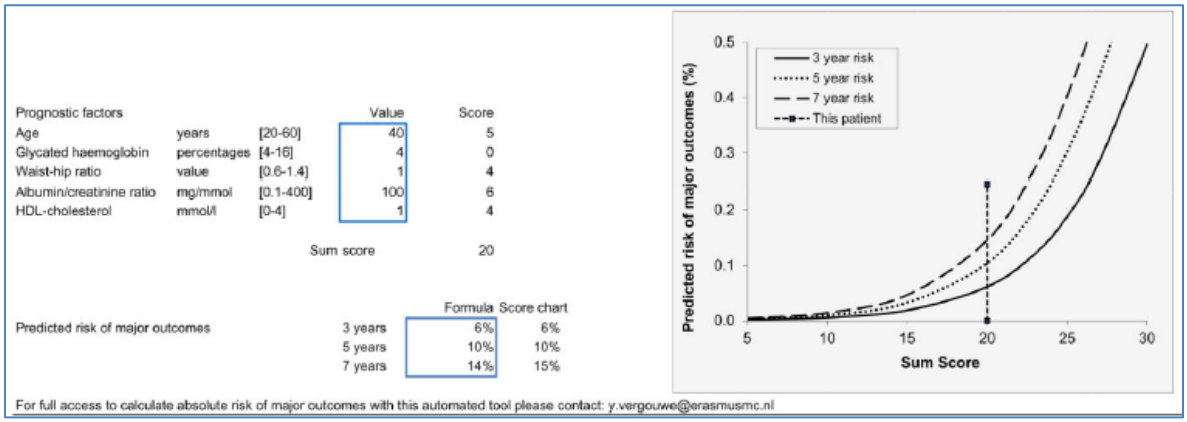
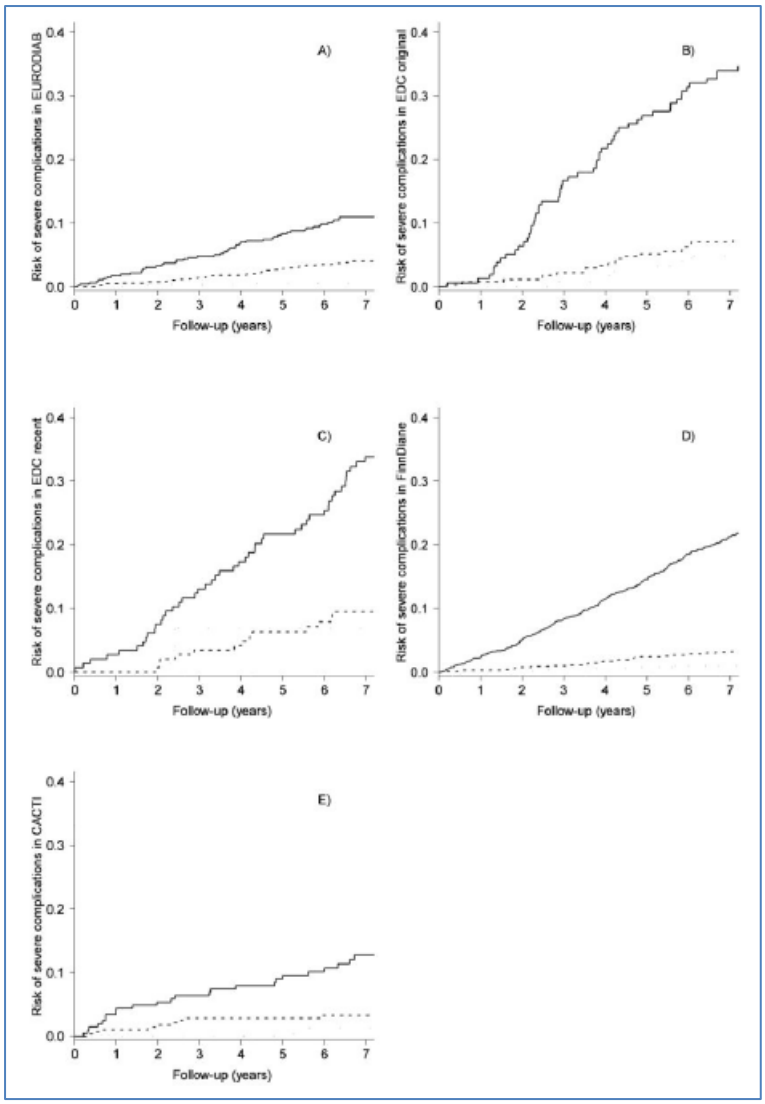


Figure 7. Left-hand figure: Prognostic Model to predict 3, 5 and 7 year risk of major outcomes in patients with type 1 diabetes. Right-hand figure: graph with 3, 5 and 7 year risk of major outcomes in patients with type 1 diabetes.

Figure 8: displays the observed Kaplan Meier risk of major outcomes divided into three score groups.



8. Observed Kaplan Meier risk of major outcomes divided into three score groups. Kaplan-Meier estimates for the risk of major outcomes. Patients are categorised based on total score (see Figure 2):8 – 15, low risk (dashed line); 16 – 20, intermediate risk; 21+, high risk (solid line).

Table 11, you can see the occurrence of severe complication for candidate prognostic factors in EURODIAB PCS.

Table 11: Occurrence of severe complication for candidate prognostic factors in EURODIAB PCS

Patient Characteristic	7-year risk of severe complication (%)	Hazard ratio (96% CI)
Age, years		
<25	3	1.0
25-34	4	1.3 (0.7 – 2.5)
35-44	7	2.7 (1.5 – 5.0)
45+	15	5.7 (2.9 – 11)
Gender		
Female	4	1.0
Male	6	1.5 (1.0 – 2.3)
Diabetes duration, years		
<5	4	1.0
5-14	4	1.1 (0.6 – 2.0)
15+	6	1.6 (0.9 – 3.0)
HbA1c, % [mmol/mol]		
< 7 [53]	3	1.0
7 – 9.9 [53–85]	4	1.5 (0.8 – 2.6)
10 + [85+]	8	2.7 (1.5 – 5.0)
Body mass index, kg/m2		
<25	4	1.0
25+	6	1.4 (0.9 – 2.2)
Waist-hip ratio		
<0.8	2	1.0
0.8-1.0	6	2.4 (1.4 – 4.0)
1.0+	10	4.2 (1.8 – 9.6)
Ever smoked		
Yes	6	1.5 (1.0 – 2.3)
No	4	1.0
Systolic pressure, mmHg		
<110	3	1.0
110-130	4	1.5 (0.9 – 2.7)
130+	8	2.8 (1.5 – 4.9)
Diastolic pressure, mmHg		
<80	4	1.0
80-90	6	1.5 (0.9 – 2.4)
90+	8	1.9 (1.1 – 3.4)
Antihypertensive medication		
Yes	10	2.3 (1.2 – 4.4)
No	4	1.0
Albumin creatinine ratio, mg/mmol		
< 0.5	4	1.0
0.5 – 1.4	3	0.9 (0.4 – 1.9)
1.5 +	7	2.0 (0.9 – 4.5)
Fasting triglyceride, mmol/l		
<1	4	1.0
1+	6	1.7 (1.1 – 2.8)
HDL, mmol/l		
< 1.2	6	1.0
1.2 – 1.5	5	0.9 (0.5 – 1.5)
1.5 +	4	0.6 (0.4 – 1.1)
Non-HDL, mmol/l		
< 3	2	1.0
3 – 5	5	2.3 (1.2 – 4.4)
5+	9	4.3 (2.1 – 8.9)

The prognostic model described in this study uses easily accessible clinical features which can discriminate between people with type 1 diabetes with good and poor prognoses. Such a prognostic model may be helpful in clinical practice and for risk stratification in clinical trials.

Larry A Distiller, Professor, Principal Physician, at the Centre for Diabetes and Endocrinology in Johannesburg sets out the clinical features that are linked to long-term survival in people with type 1 diabetes, allowing identification of these individuals. Recognising these individuals will aid in assessing prognosis and treating the identified risk factors could improve survival. (Distiller, 2014)

Distiller observes that good glycaemic control alone cannot explain why some type 1 patients survive into old age.

Lipids - There is a clear relationship between the level of glycaemic control and lipid abnormalities, with an independent correlation between HbA1c and low-density lipoprotein (LDL)-cholesterol, non-high-density lipoprotein (HDL) cholesterol and triglycerides.

Blood Pressure - Hypertension in those with type 1 diabetes is often a manifestation of underlying nephropathy. However, hypertension can also occur as a stand-alone risk factor (non-renal hypertension). In type 1 diabetes, hypertension without nephropathy has been shown to be a major risk factor for the development of carotid artery plaque. It, therefore, appears as though hypertension itself, while a significant risk factor for CVD, if treated does not mitigate against longevity in this population.

Microvascular Disease - The presence of diabetic nephropathy, microalbuminuria or macroalbuminuria is a significant risk factor for coronary artery disease (CAD), cardiovascular mortality and all-cause mortality, and there is a strong independent relationship between albuminuria and CAD. The occurrence of stroke in subjects with type 1 diabetes is also increased by the presence of nephropathy.

The long-term risk of a reduction in estimated glomerular filtration rate (eGFR) is also shown to be 50% lower among those who are treated early in the course of type 1 diabetes with intensive diabetes therapy than among those treated with conventional diabetes therapy. Good glycaemic control in the early years of diabetes may be more important when achieved in those who have had the condition for some years. It is therefore apparent that those individuals with type 1 diabetes who are likely to survive would remain free of any evidence of nephropathy.

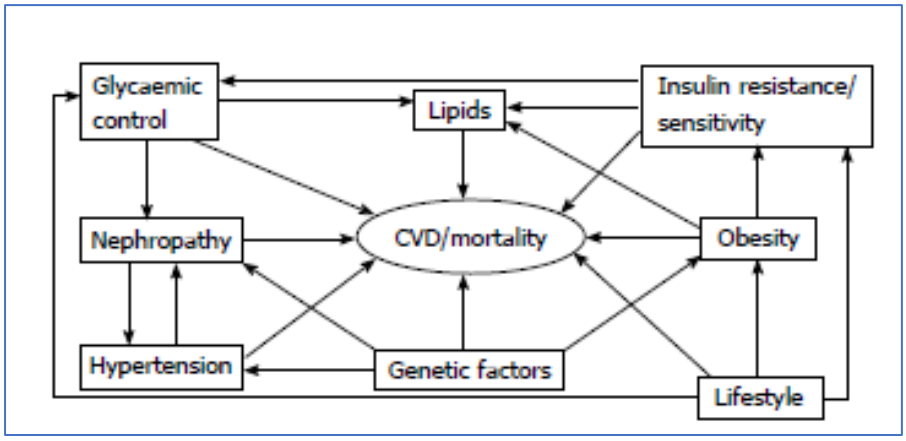
No prospective studies in people with type 1 diabetes have found a strong association between retinopathy and CVD or mortality. However, the presence of retinopathy increases the risk of stroke. Retinopathy is probably not a major risk factor for CVD or mortality in those with type 1 diabetes, as opposed to those with type 2 diabetes where the presence of retinopathy may indicate CAD and mortality risk.

The Metabolic Syndrome - There is no reason to expect people with type 1 diabetes to have a lower prevalence of obesity and metabolic syndrome (MetS) than the general population and a MetS frequency in people with type 1 diabetes of over 30% has been reported. A significant relationship exists between mortality and central obesity in those with type 1 diabetes and type 1 subjects with the MetS have been shown to have an increased prevalence of the macrovascular disease. Identifying people with the MetS in the presence of type 1 diabetes is difficult.

Genetic Factors - Clearly, a complex interaction exists between multiple risk factors in determining which people with type 1 diabetes are likely to live into older age. However, these people can often be identified clinically based on a combination of factors (Figure 9).

In conclusion, while the longevity of those with type 1 diabetes has improved considerably over the past century, these people remain with a reduced life expectancy compared to the non-diabetic population. Nevertheless, a subgroup of these individuals may survive into older age despite their diabetes. Certain clinical and biochemical features can identify these people.

Figure 9: Complex interactions exist between multiple risk factors in determining the outcome for patients with type 1 diabetes



5.2.2 Newer Technologies

Tauschmann et al (Tauschmann et al., 2018) published the results of a 12-week randomised trial which assessed the effectiveness of day-and-night hybrid closed-loop insulin delivery compared with sensor-augmented pump therapy in people with sub optimally controlled type 1 diabetes aged 6 years and older.

Closed-loop insulin delivery systems (the artificial pancreas), couple continuous glucose monitoring and algorithm-directed insulin pump delivery.

Participants in the Tauschmann study were recruited from diabetes outpatient clinics at four hospitals in the UK and two centres in the USA. The trial randomly assigned participants with type 1 diabetes aged 6 years and older treated with insulin pumps and with suboptimal glycaemic control (glycated haemoglobin [HbA1c] 7.5–10.0%) to receive either hybrid closed-loop therapy or sensor-augmented pump therapy over 12 weeks of free living.

Participants with HbA1c outside the range of 7.5–10.0% and other groups, such as those with impaired awareness of hypoglycaemia or a history of recurrent severe hypoglycaemia were excluded.

From May 12, 2016, to Nov 17, 2017, 114 individuals were screened, and 86 eligible patients were randomly assigned to receive hybrid closed-loop therapy (n=46) or sensor-augmented pump therapy (n=40; control group).

The trial showed that 12-week use of a day-and-night hybrid closed-loop insulin delivery system, compared with sensor-augmented insulin pump therapy, was associated with an improvement in overall glucose control and a reduction in hypoglycaemia risk in sub optimally controlled type 1 diabetes in children aged 6 years and older, adolescents, and adults.

The use of hybrid closed-loop therapy led to a modest, but clinically significant, 0.36% reduction in HbA1c, compared with sensor-augmented pump therapy. (Table 12). Improvements in HbA1c were consistent across all age groups. Results from this study together with those from previous studies support the adoption of closed-loop technology in clinical practice across all age groups.

Table 12: Comparison of day-and-night glucose control during closed-loop and control periods

	Baseline		12 weeks		Difference (95% CI)*	p value*
	Closed-loop (n=46)	Control (n=40)	Closed-loop (n=46)	Control (n=40)		
Percentage of time with sensor glucose concentration in range						
3·9 to 10·0 mmol/L†	52% (10)	52% (9)	65% (8)	54% (9)	10·8 (8·2 to 13·5)	<0·0001
Less than 3·9 mmol/L	3·5% (2·0 to 5·4)	3·3% (1·2 to 5·5)	2·6% (1·9 to 3·6)	3·9% (1·7 to 5·3)	−0·83 (−1·40 to −0·16)‡	0·0130
Less than 3·5 mmol/L	1·8% (0·8 to 3·2)	1·9% (0·6 to 3·3)	1·4% (0·9 to 1·9)	2·0% (0·9 to 3·0)	−0·33 (−0·81 to 0·04)‡	0·08
Less than 2·8 mmol/L	0·4% (0·1 to 1·0)	0·5% (0·1 to 1·0)	0·3% (0·2 to 0·6)	0·5% (0·2 to 0·9)	−0·09 (−0·24 to 0·01)‡	0·11
More than 10·0 mmol/L	44% (11)	44% (11)	32% (8)	42% (10)	−10·3 (−13·2 to −7·5)	<0·0001
More than 16·7 mmol/L	5·5% (3·3 to 8·3)	4·9% (2·7 to 7·3)	3·5% (1·9 to 4·6)	4·4% (2·9 to 6·5)	−1·42 (−2·20 to −0·69)‡	<0·0001
Glycated haemoglobin						
Percentage	8·0% (0·6)	7·8% (0·6)	7·4% (0·6)	7·7% (0·5)	−0·36% (−0·53 to −0·19)	<0·0001
mmol/mol of non-glycated haemoglobin	63 (7)	62 (6)	57 (7)	60 (6)	−4·0 (−5·8 to −2·2)	<0·0001
Glucose AUC less than 3·5 mmol/L§	11 (5 to 25)	12 (4 to 25)	9 (5 to 15)	13 (6 to 23)	−2·3 (−5·4 to 0·3)‡	0·08
Glucose, mmol/L	9·8 (1·1)	9·8 (1·1)	8·9 (0·7)	9·7 (1·0)	−0·82 (−1·06 to −0·57)	<0·0001
SD of sensor glucose, mmol/L	3·9 (0·5)	3·8 (0·5)	3·5 (0·5)	3·8 (0·5)	−0·35 (−0·48 to −0·22)	<0·0001
Coefficient of variation of sensor glucose	40% (5)	39% (5)	40% (4)	40% (4)	−0·4% (−1·4 to 0·7)	0·50
Total insulin, U/kg per day	0·75 (0·22)	0·70 (0·18)	0·81 (0·25)	0·71 (0·19)	0·031 (−0·005 to 0·067)	0·09
Total basal insulin, U/kg per day	0·32 (0·07)	0·31 (0·08)	0·46 (0·13)	0·32 (0·10)	0·124 (0·099 to 0·150)	<0·0001
Total bolus insulin, U/kg per day	0·43 (0·19)	0·39 (0·14)	0·34 (0·17)	0·39 (0·13)	−0·087 (−0·114 to −0·060)	<0·0001
Bodyweight change from screening, kg	NA	NA	2·2 (2·3)	1·4 (2·6)	0·68 (−0·34 to 1·69)	0·19
PedsQL total score (participant version)	74 (12)	76 (14)	76 (12)	77 (12)	−0·3 (−4·1 to 3·4)	0·85
PedsQL total score (parent version)	69 (14), n=22	70 (15), n=19	74 (13), n=21	72 (11), n=19	3·0 (−2·7 to 8·7)	0·29

Data are mean (SD) or median (IQR). NA=not applicable. PedsQL=Pediatric Quality of Life Inventory. *Model adjusted for baseline HbA_{1c}, baseline value of the metric and site as a random effect. Difference is closed-loop minus control. †Primary endpoint. ‡Point estimates and CIs for metrics with a skewed distribution constructed from the rank test. §The area under the curve (AUC) is for a glucose level of less than 3·5 mmol/L per 24-h period.

Relatively new technology in the management of type 1 diabetes is that of continuous or real time glucose monitoring (rtCGM). The effectiveness of this technology has been assessed in a number of studies and one published in 2017 (Heinemann et al., 2018) reported that usage of rtCGM reduced the number of hypoglycaemic events in individuals with type 1 diabetes treated by multiple daily insulin injections and with impaired hypoglycaemia awareness or severe hypoglycaemia. In fact, it was observed in this multicentre, open-label, parallel, randomised controlled trial that the mean number of hypoglycaemic events per 28 days among participants in the rtCGM group was reduced from 10.8 (SD 10.0) to 3.5 (4.7); reductions among control participants were negligible (from 14.4 [12.4] to 13.7 [11.6]).

Incidence of hypoglycaemic events decreased by 72% for participants in the rtCGM group (incidence rate ratio 0·.8 [95% CI 0.20–0.39], p<0.0001).

The area of digital health technologies has been developing rapidly to help people manage their diabetes. This could lead to a more optimal management of diabetes in the future. However, it is too early to say how effective these technologies are for a range of issues ranging from inadequate evidence on app accuracy and clinical validity to lack of training provision, poor interoperability and standardization, and insufficient data security. (Alexander Fleming et al., 2020)

5.2.3 Conclusion

Increased morbidity is understood to be a risk factor in those with type 1 diabetes; known microvascular, macrovascular and neuropathic complications are directly linked to glycaemic control.

There is emerging evidence that new medical devices can help people manage their diabetes better potentially leading to more stable glycaemic control and a reduction in the risk of developing complications of diabetes.

While the longevity of those with type 1 diabetes has improved considerably over the past century, these individuals still experience reduced life expectancy compared to a non-diabetic population. Nevertheless, a subgroup of these individuals may survive into older age despite their diabetes. Certain clinical and biochemical features can identify these people.

5.3 Diabetes and morbidity – Type 2

5.3.1 Introduction

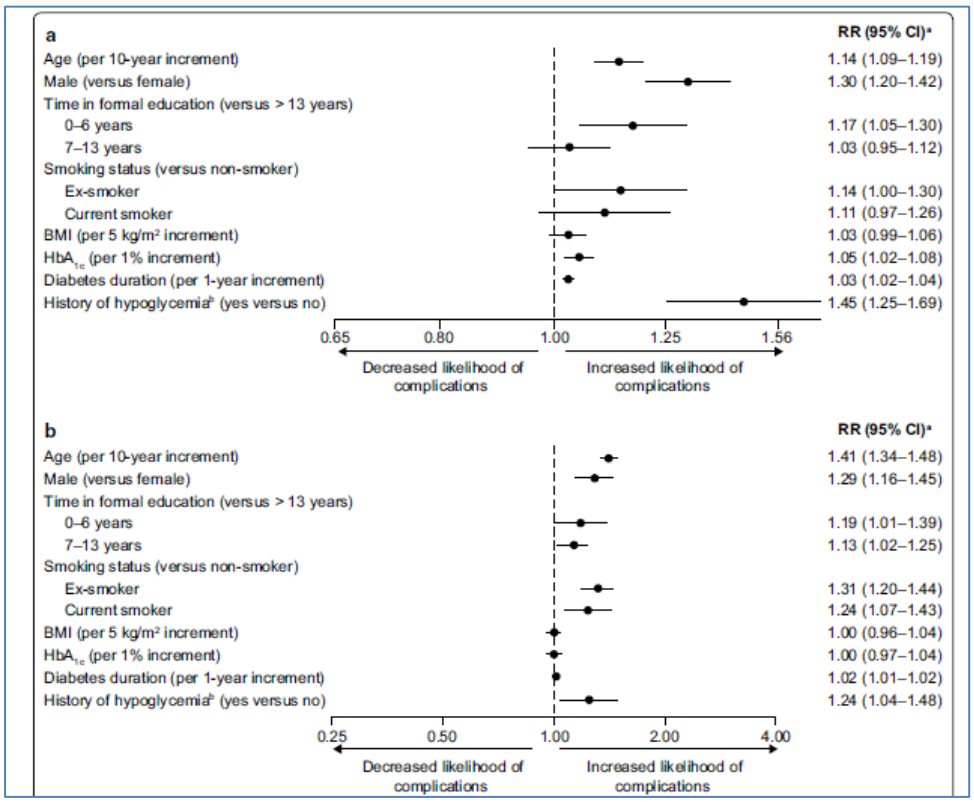
As previously described, people with diabetes are at increased risk of developing several complications as a result of inadequately controlled blood glucose levels. These include damage to the blood vessels and damage to nerves which in turn give rise to retinopathy, kidney disease and cardiovascular disease. As a result, there are several studies that seek to understand the prevalence of complications in people with diabetes, and the risk factors associated with them.

5.3.2 Research findings

One such study is DISCOVER, a global, prospective, observational study program of 15,992 patients with type 2 diabetes initiating second-line therapy, conducted across 38 countries This study provides useful insights into the prevalence of complications in those living with type 2 diabetes. This analysis (Kosiborod et al., 2018) reports that when standardized for age and sex, the highest prevalence of microvascular and macrovascular complications was found in Europe, where patients also had the highest mean BMI and blood pressure, which are important cardiovascular risk factors.

Figure 10 displays the likelihood of developing complications according to known risk factors.

Figure 10: Multivariable analysis of factors associated with a) microvascular and b) macrovascular complications



Similar factors were found to have a statistically significant positive association with the prevalence of both microvascular and macrovascular complications. These included age, male sex, having a low level of education, duration of diabetes since diagnosis, and having a history of any hypoglycemic event (minor event in the previous month or major event in the previous year).

In a cohort study published in 2015, (Shah et al., 2015) researchers examined the associations between type 2 diabetes and 12 initial manifestations of cardiovascular disease. The study cohort included 1,921,260 individuals, of whom 1,887,062 (98.2%) did not have diabetes and 34,198 (1.2%) had type 2 diabetes.

For individuals aged 40 years without cardiovascular disease, the overall estimated risk of developing any cardiovascular disease by age 80 years was 30.7% for women without diabetes and 44.3% for men without diabetes, compared with 58.2% for women with type 2 diabetes and 67.4% for men with type 2 diabetes. Indeed, both biological and psychosocial factors have been found to be responsible for sex and gender differences in diabetes risk and outcome.(Kautzky-Willer et al., 2016)

Harding et al (Harding et al., 2019) report that globally, known diabetes-related complications such as rates of lower extremity amputations, (LEAs), acute complications, CVD, all-cause mortality and CVD mortality among people with diabetes are generally declining, though there are some notable exceptions.

The epidemiology of chronic kidney disease (CKD) as a result of type 2 diabetes has been reported in a study using data from the GBD (Global Burden of Disease) study (Li et al., 2021). The study aimed to evaluate how the burden of CKD (chronic kidney disease), because of T2DM, has changed over time (between 1990 and 2017) and geographic location.

The incident cases of CKD because of T2DM worldwide were reported to have increased by 74% (95% CI 37–92) from 1990 to 2017. The age-standardized incidence rate (ASIR) decreased by an average of 0.40% (95% CI -0.47 to -0.33) per year during the same period.

Rodríguez-Poncelas et al (Rodríguez-Poncelas et al., 2016) have also examined the interaction between CKD and another known complication of diabetes, retinopathy, and report that CKD is associated with a higher rate of Diabetic Retinopathy (DR) (Odds ratio [OR], 1.5). It is likely that there are complex interactions between the known complications due to their shared pathology.

Indeed, Smith et al (Smith et al., 2020) provide some valuable insights, through analysis to determine factors associated with progression to referable diabetic retinopathy in people with type 2 diabetes in the Republic of Ireland. It was observed that higher current values of HbA1c, systolic BP and triglycerides were associated with higher risk of referral.

5.3.3 Conclusion

The risk factors that drive the development of complications in type 2 diabetes are broadly similar to those for type 1 diabetes. At the core is inadequate glycaemic control as it is from this that all microvascular and macrovascular complications arise. The additional morbidity burden cannot be underestimated; this includes retinopathy which can lead to blindness, nerve and blood vessel damage that can lead to amputation and major CVD.

5.4 Prediabetes

5.4.1 Introduction

Prediabetes, typically defined as blood glucose levels above normal but below diabetes thresholds, is a risk state that defines a high chance of developing diabetes. It is an intermediate metabolic state between normoglycaemia and diabetes and includes those with impaired glucose tolerance and impaired fasting glucose.

Diagnostic criteria for prediabetes have changed over time and currently vary depending on the institution. Table 13 displays the parameters by which pre-diabetes is defined by NICE in the UK. (NICE, n.d.-b)

Table 13: Diagnostic criteria for diabetes and prediabetes

	Normal	**Pre-diabetes**	**Diabetes**
FPG	<5.5 mmol/l	5.5-7.0 mmol/l	>7.0 mmol/l
OGTT	<7.8mmol/l	7.8-11.1 mmol/l	>11.1 mmol/l
HbA1C	<6.0%	6.0-6.4%	>6.4%

FPG = Fasting Plasma Glucose. OGTT = Oral Glucose Tolerance Test

The prevalence of prediabetes is increasing worldwide and is associated with the simultaneous presence of insulin resistance and β-cell dysfunction, abnormalities that start before glucose changes are detectable.

It has been observed that a proportion of individuals with prediabetes will progress to diabetes, but there is also a possibility that some may, in fact, regress to normoglycemia (usually because of changes made to lifestyle behaviours such as increased physical activity and dietary changes.) Tabak et al (Tabák et al., 2009) suggest that there is an annualised conversion rate from prediabetes to diabetes of 5-10% and that a similar proportion convert back to normoglycaemia.

There has been some criticism of the term ‘prediabetes’, not least that there is a concern that it may falsely indicate a lack of disease, (when it is known that glucose metabolism is already disturbed), and equally, some do not progress to diabetes. However, it is accepted that there is a metabolic state in which glucose metabolism and insulin sensitivity are disordered regardless of how this state is classified.

It has been noted that the parameters used to classify ‘prediabetes’ may differ between ethnic groups, and different age groups. Of particular note is that there is evidence that abnormalities start before glucose changes are detectable e.g., the presence of insulin resistance and b-cell dysfunction.

For prediabetic individuals, lifestyle modification is the cornerstone of diabetes prevention with evidence of 40-70% relative risk reduction. Data also suggests potential benefits from pharmacotherapy. (Tabák et al., 2012a)

Considering that prediabetes is a metabolic state in which an individual has an increased risk of progressing to diabetes, it would be safe, therefore, to assume that the whole risk profile for diabetes is progressive, from a non-diabetic, to a prediabetic state, and eventually, for some, a diagnosis of diabetes. It is of interest to the WP to understand the pathway to prediabetes so that all risk factors can be understood.

5.4.2 Review

Longitudinal studies can provide the type of data that following analysis will help us to understand the nature of prediabetes and those who are at risk. Whitehall II is a longitudinal, prospective cohort study of 10,308 women and men, all of whom were employed in the London offices of the British Civil Service at the time they were recruited to the study in 1985. The Study is led by Professor Mika Kivimaki at University College London. The initial data collection included a clinical examination and self-report

questionnaire. Since then, twelve waves of data collection have been completed. Analysis of this dataset has revealed some of the factors that indicate the potential to progress to prediabetes.

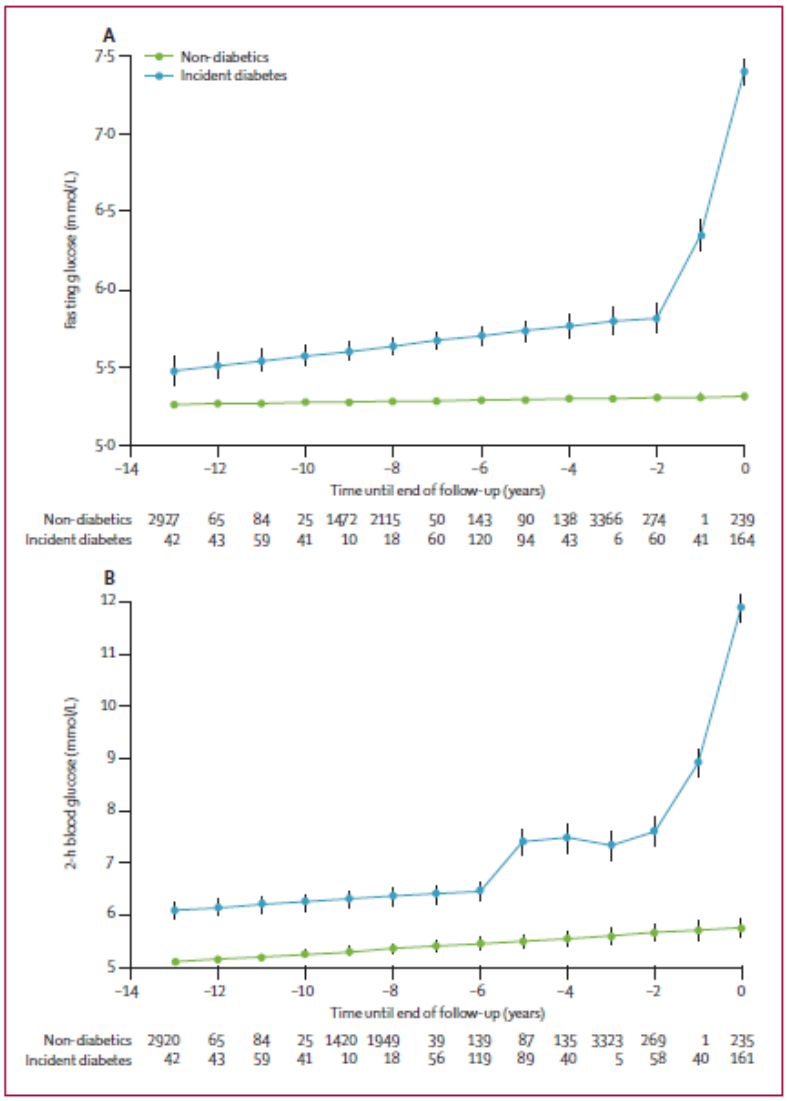
Back in 2009, a team of researchers analysed data from the Whitehall II cohort, and aimed to characterise trajectories of fasting and post-load glucose, insulin sensitivity, and insulin secretion in individuals who develop type 2 diabetes.(Tabak et al., 2009)

They report that in those with diabetes, the trajectory towards becoming diabetic was initially linear, but started to increase with steep quadratic increases of blood glucose 3-6 years before the diagnosis of type 2 diabetes. Similarly, adverse changes in insulin sensitivity, and insulin secretion were also observed up to 6 years before the diagnosis of diabetes. Figure 11 displays these trajectories.

In a 2013 publication, a team comprised of largely the same researchers examined trajectories of cardiometabolic risk factors and 10-year cardiovascular risks in the prospective Whitehall II study cohort. In particular, they wished to examine whether patients diagnosed on the basis of fasting glucose concentrations, those diagnosed on the basis of 2-hour concentrations, and those diagnosed on the basis of both criteria differed in terms of pathogenesis or cardiovascular risks. (Færch et al., 2013)

After a median follow-up of 14.2 years, it was observed that underlying pathogenesis differed as much as 18 years before diagnosis between patients with type 2 diabetes diagnosed based on increased fasting glucose concentrations, those diagnosed based on 2 h concentrations, and those diagnosed based on both criteria. The researchers suggest that further studies should establish whether glycaemic control, drug needs, and the incidence of cardiovascular disease and microvascular complications differ between patients with different subgroups of disease.

Figure 11: Fasting (A) and 2-h postload (B) glucose trajectories before the diagnosis of diabetes or the end of follow-up



The numbers are 505 incident diabetes cases and 6033 non-diabetics. Time 0 is the diagnosis for incident diabetes cases or end of follow-up for non-diabetics. Multilevel longitudinal modelling was done using a linear growth model for non-diabetic and piecewise approach, including cubic terms for time, for incident diabetic individuals with oral glucose tolerance test fasting glucose (A) and 2-h glucose (B) as outcomes. Analysis was adjusted for age, sex, ethnic origin, and study phase. Estimations were done for a hypothetical population consisting of 71% male, 91% white individuals aged 63 years at time 0 years. Error bars show 95% CI for the fixed effects. Tables show the number of measurements for each year at and before diabetes diagnosis or the end of follow-up.

Subsequently, in 2013, the core team again turned to the Whitehall II study to identify different patterns of obesity, starting from a diabetes-free population over a development period of 18 years, to better understand the heterogeneity of diabetes. (Vistisen et al., 2014) Other metabolic risk factors were also examined accompanying each pattern of obesity, and these included trajectories of insulin resistance as well as other cardiometabolic risk factors.

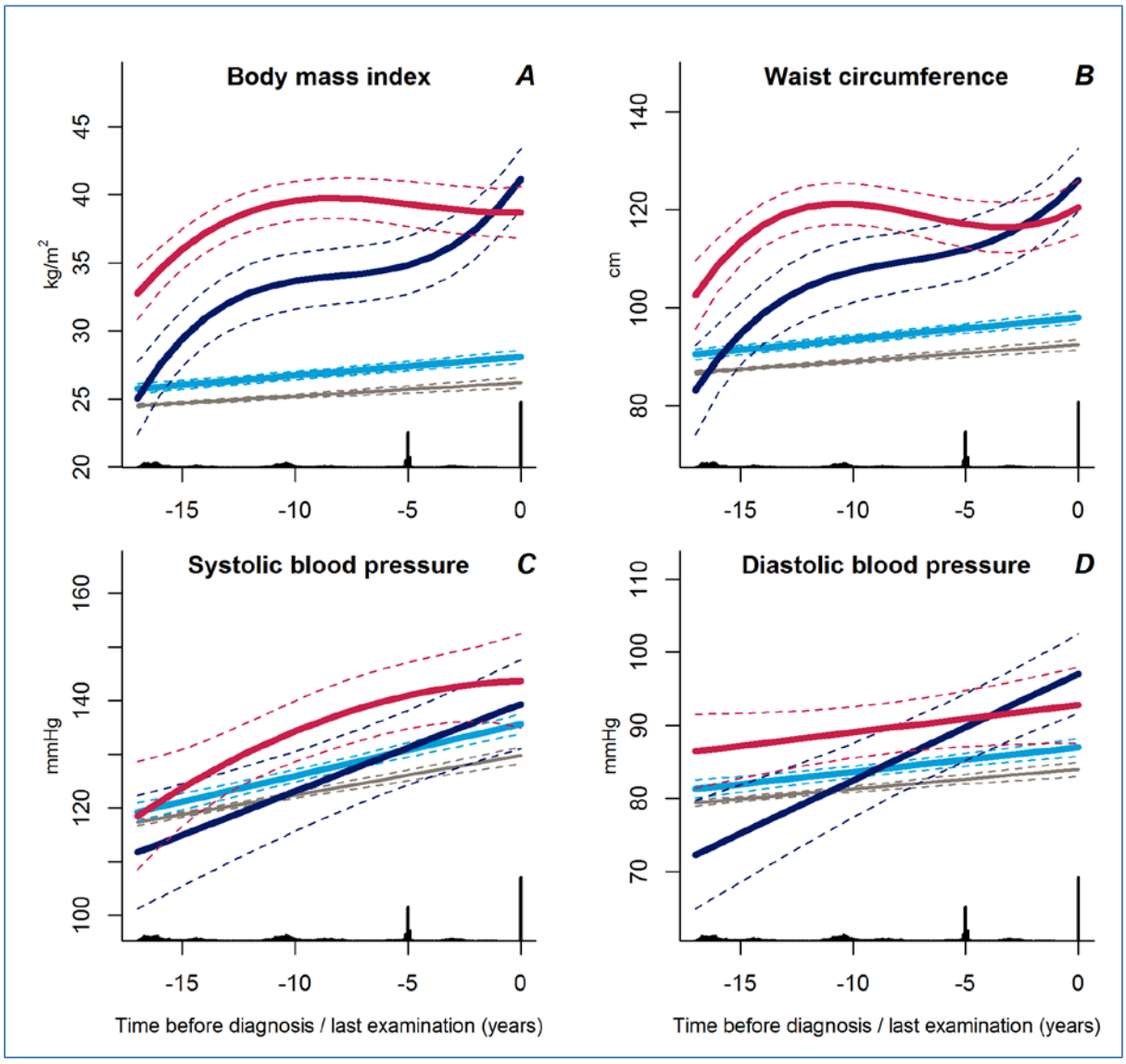
White men and women, initially free of diabetes, were followed with 5-yearly clinical examinations from 1991–2009 for a median of 14.1 years.

Three patterns of obesity changes prior to diagnosis were identified:

1. Stable overweight (largest group, 94%)
2. Progressive weight gain
3. Persistently obese

This is displayed in Figure 12**,** which shows the trajectories for a hypothetical male of 60 years at time 0 of body mass index (A), waist circumference (B), systolic blood pressure (C), and diastolic blood pressure (D) from 18 years before the time of diagnosis/the last examination. Trajectories for blood pressure represent a person not on anti-hypertensive treatment. Solid lines indicate estimated trajectories for each group and dashed lines are 95% confidence limits. Black bars at the bottom indicate the relative data distribution over the follow-up period. (Light blue = stable overweight; dark blue = progressive weight gain; red = persistently obese; grey = diabetes-free population.)

Figure 12: Trajectories for a hypothetical male of 60 years at time 0 of body mass index (A), waist circumference (B), systolic blood pressure (C), and diastolic blood pressure (D) from 18 years before time of diagnosis/last examination



It was observed overall that prior to diagnosis the great majority of patients had modest weight gains. In fact, five years prior to diagnosis there was a rapid increase in FPG and 2-hour plasma glucose

measures. The “progressive weight gain” category increased more rapidly compared to the “stable overweight” category.

A higher proportion of diabetes was diagnosed by GP’s for people that were morbidly obese compared to overweight individuals. This suggests that GP’s will tend to focus screening on the morbidity obese.

Findings also support the “prevention paradox” in that a larger number of people exposed to low risk is likely to produce more cases that focus on the few most obese individuals. These results suggest that strategies focusing on small weight reductions for the entire population may be more beneficial than focusing on weight loss for high-risk individuals and highlight again the heterogenous nature of prediabetes.

Individuals with prediabetes may also be at increased risk of cardiovascular disease, even without a diagnosis of diabetes. A 2010 systematic review (Ford et al., 2010) describes a modest but increased risk of cardiovascular disease in those with impaired fasting glucose and IGT. A combined IFG and IGT (5 publications), fixed effect summary RR was estimated to be 1.10 (95th CI: 0.99-1.23).

The results of an additional systematic review and meta-analysis that sought to evaluate associations between different definitions of prediabetes and the risk of cardiovascular disease and all-cause mortality published in 2016 are set out in Figure 13, Figure 14 and Figure 15 (Huang et al., 2016)

Twenty-five studies reported data on the association between prediabetes and the risk of all-cause mortality (Figure 13). Random effects models analyse shows that prediabetes was associated with an increased risk of all-cause mortality: IFG-ADA (relative risk 1.13, 95% confidence interval 1.02 to 1.25), IFG-WHO (1.13, 1.05 to 1.21), impaired glucose tolerance (1.32, 1.23 to 1.40).

Prediabetes was not associated with an increased risk of all-cause mortality when it was defined as HbA1c.

Figure 13: Association between prediabetes and risk of all-cause mortality.

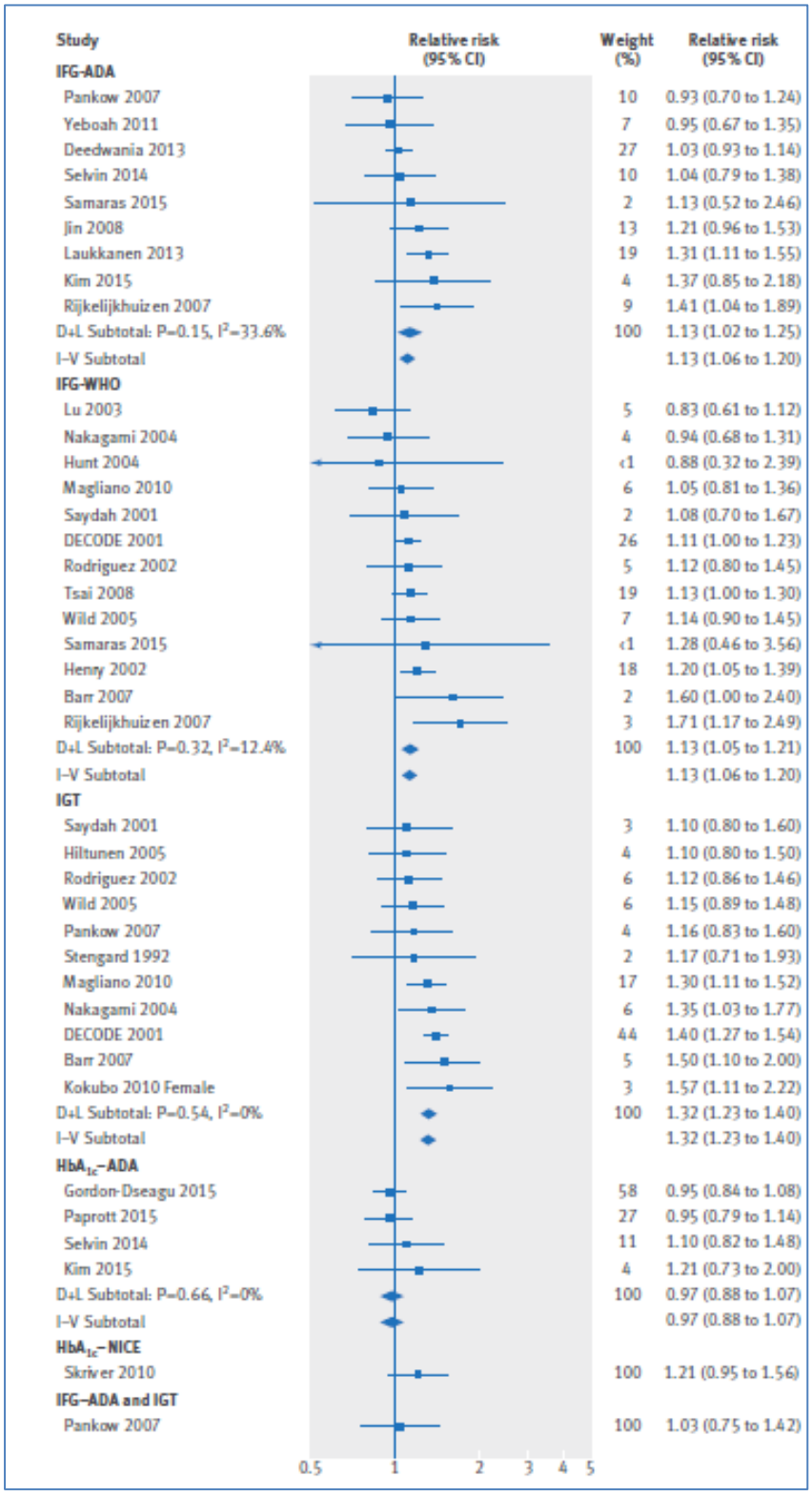


Figure 13

D+L=DerSimonian and Laird random effects models;

HbA1c-ADA=prediabetes defined as raised HbA1c according to American Diabetes Association (ADA) criteria (39-47 mmol/mol);

HbA1c-NICE=prediabetes defined as raised HbA1c according to NICE guidance (42-47 mmol/mol);

IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L);

IFG-WHO=IFG according to WHO criteria (6.1-6.9 mmol/L);

IGT =impaired glucose tolerance; I-V=inverse variance fixed effects models

Thirty-five studies reported data for the association between prediabetes and risk of composite cardiovascular disease. Random effects models analyse showed that prediabetes was associated with increased composite cardiovascular events when it was defined as IFG-ADA (relative risk 1.13, 95% confidence interval 1.05 to 1.21), IFG-WHO (1.26, 1.12 to 1.41), impaired glucose tolerance (1.30, 1.19 to 1.42), HbA1c 38.8-46.4 mmol/mol (1.21, 1.01 to 1.44), or HbA1c 42.11-46.4 mmol/mol (1.25, 1.01 to 1.55) (Figure 14).

Figure 14: Association between prediabetes and composite cardiovascular events.

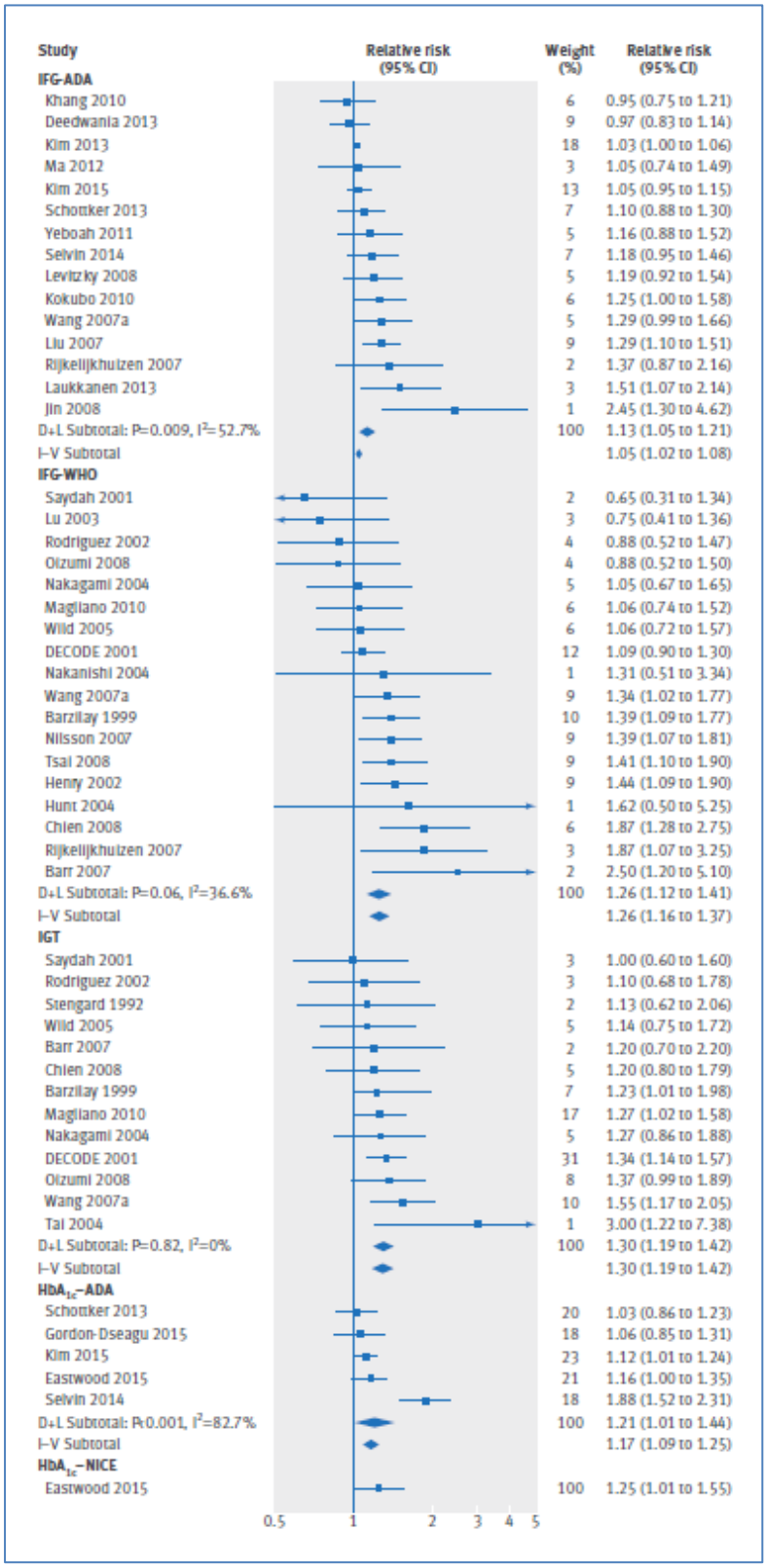


Figure 14

D+L=DerSimonian and Laird random effects models;

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HbA1c-NICE=prediabetes defined as raised HbA1c according to NICE guidance (42-47 mmol/mol);

IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L);

IFG-WHO=IFG according to WHO criteria (6.1-6.9 mmol/L);

IGT =impaired glucose tolerance; I-V=inverse variance fixed effects models

Twenty-four studies reported data for the association between prediabetes and risk of coronary heart disease. Similar to results for composite cardiovascular events, prediabetes was associated with increased risk of coronary heart disease. (Figure 15)

Figure 15: Association between prediabetes and risk of coronary heart disease.

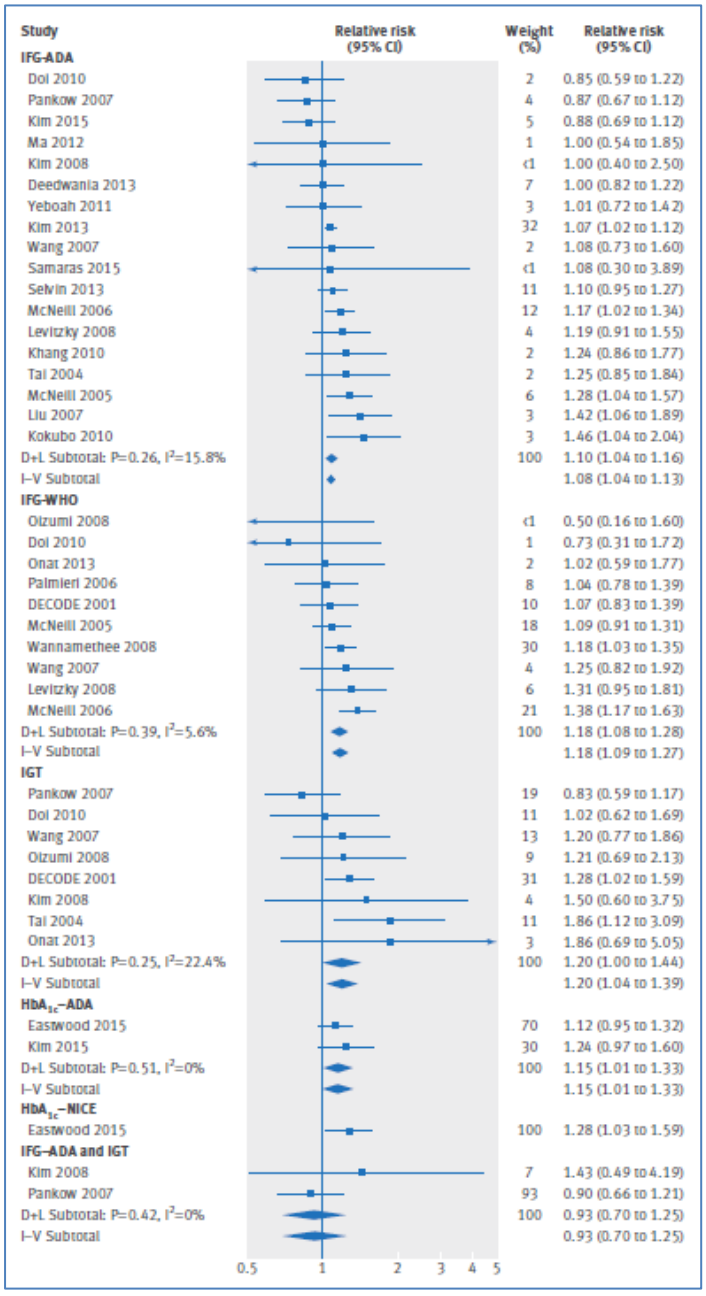


Figure 15

D+L=DerSimonian and Laird random effects models;

HbA1c-ADA=prediabetes defined as raised HbA1c according to American Diabetes Association (ADA) criteria (39-47 mmol/mol);

HbA1c-NICE=prediabetes defined as raised HbA1c according to NICE guidance (42-47 mmol/mol);

IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L);

IFG-WHO=IFG according to WHO criteria (6.1-6.9 mmol/L);

IGT =impaired glucose tolerance;

I-V=inverse variance fixed effects models

Eighteen studies reported data on the association between prediabetes and the risk of stroke. Combined data showed that IFG-ADA (relative risk 1.06, 95% confidence interval 1.01 to 1.11), IFG-WHO (1.17, 1.09 to 1.25), or impaired glucose tolerance (1.20, 1.0 to 1.45) were associated with an increased risk of stroke after multivariate adjustment. The risk of stroke, however, was not significant in studies that defined prediabetes as raised HbA1c. (Figure 16)

In this meta-analysis, prediabetes defined as impaired glucose tolerance or impaired fasting glucose was associated with an increased risk of cardiovascular disease and all-cause mortality. The risk increased in people with a fasting glucose concentration as low as 5.55 mmol/L. In addition, an HbA1c of 39-47 mmol/mol or 42-47 mmol/mol was associated with an increased risk of composite cardiovascular disease and coronary heart disease.

The researchers conclude that there is a case for a lower cut-off for impaired fasting glucose according to ADA criteria as well as the incorporation of HbA1c in defining prediabetes.

Figure 16: Association between prediabetes and risk of stroke

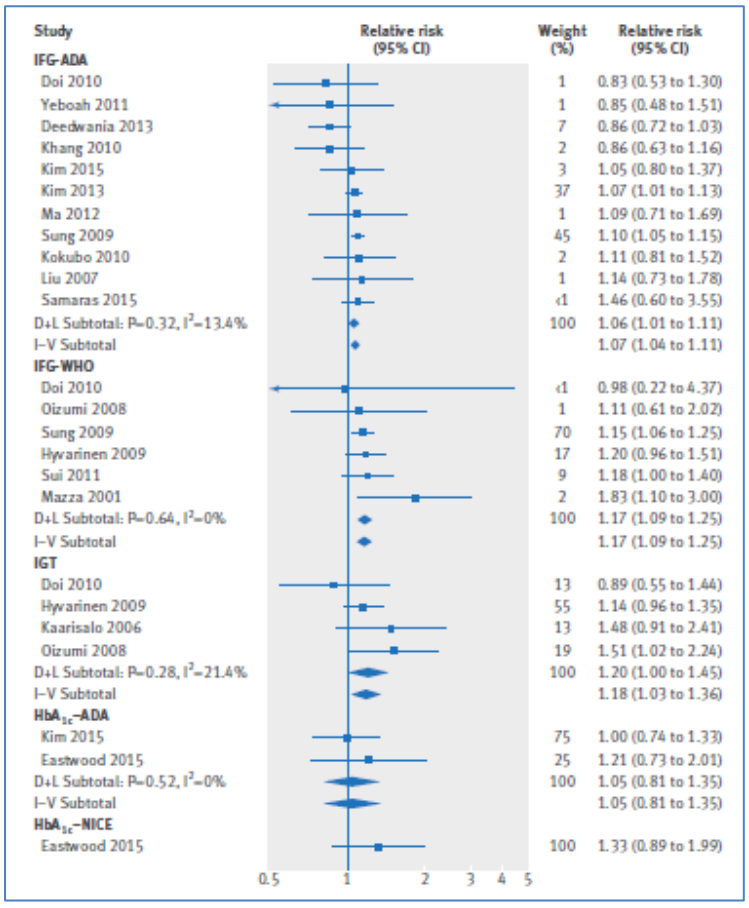


Figure 16

D+L=DerSimonian and Laird random effects models;

HbA1c-ADA=prediabetes defined as raised HbA1c according to American Diabetes Association (ADA) criteria (39-47 mmol/mol);

HbA1c-NICE=prediabetes defined as raised HbA1c according to NICE guidance (42-47 mmol/mol);

IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L);

IFG-WHO=IFG according to WHO criteria (6.1-6.9 mol/L);

IGT =impaired glucose tolerance; I-V=inverse variance fixed effects models

We've seen how increasing glucose dysregulation, even before a diagnosis of diabetes, can carry excess disease and mortality risk. A study published in 2014 sought to examine whether regression to normal glucose regulation (NGR) is also associated with a long-term decrease in cardiovascular disease (CVD) risk. (Perreault et al., 2014)

Data from the analysis was drawn from the Diabetes Prevention Program Outcomes Study (DPPOS). Participants included 2,775 persons categorised as at high risk for diabetes (as of data lock on 10 July 2013).

The researchers wanted to compare the following indicators between those who returned to NGR at least once during 10 years' follow-up time against those who either remained with prediabetes or had diabetes developed within the period:

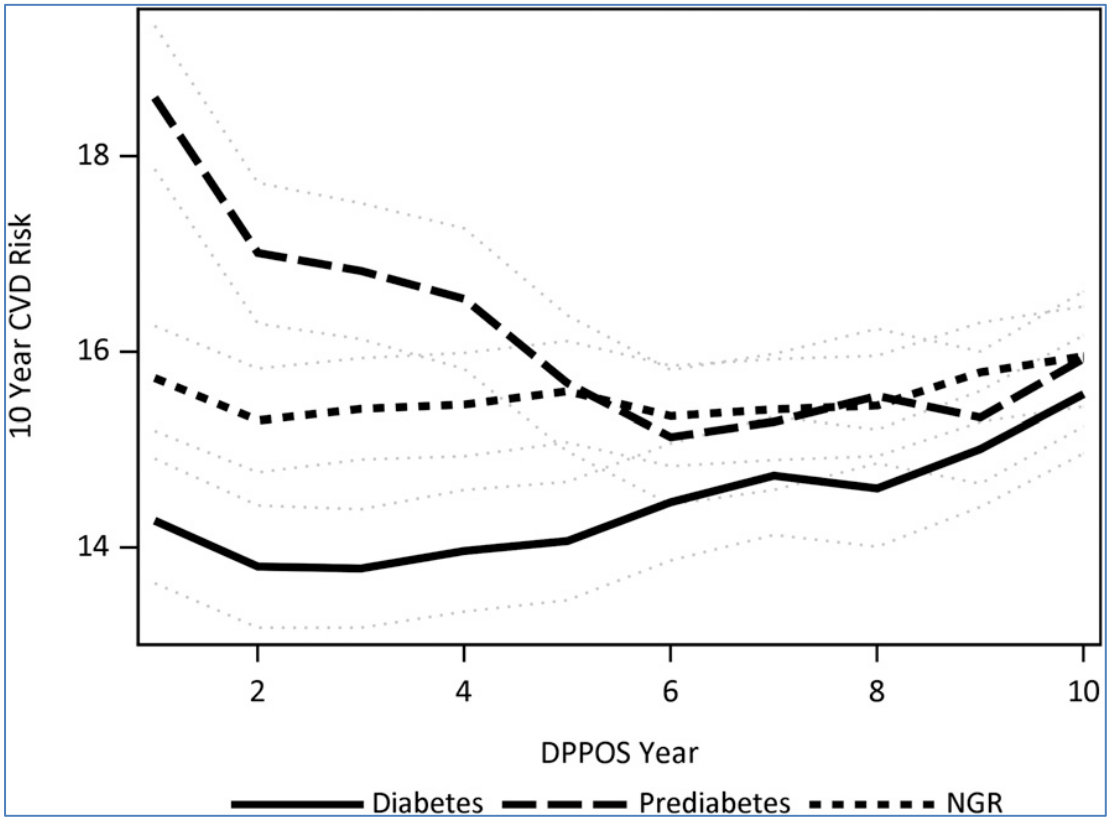
- Estimate of the global 10-year CVD risk (Framingham 2008 score)
- Individual CVD risk factors

During 10 years of follow-up, the mean Framingham 10-year CVD risk scores were highest in the prediabetes group (16.2%), intermediate in the NGR group (15.5%), and 14.4% in people with diabetes (all pairwise comparisons $P < 0.05$), but scores decreased over time for those people with prediabetes (18.6% in year 1 vs. 15.9% in year 10, $P < 0.01$). The trajectory of estimated 10-year CVD risk over the course of the DPPOS, in groups defined by glycaemic status in the DPP, is depicted in Figure 17.

The lower score in the diabetes group versus other groups, a declining score in the prediabetes group, and favourable changes in each individual risk factor in all groups was explained, in part, by higher or increasing medication use for lipids and blood pressure.

Prediabetes represents a high-risk state for CVD. Restoration of NGR and/or medical treatment of CVD risk factors can significantly reduce the estimated CVD risk in people with prediabetes.

Figure 17: Trajectories of 10-year CVD risk during the DPPOS in people with diabetes (solid), prediabetes (medium dash), and NGR (short dash) represented by means (lines) and 95% CIs (grey dotted line) with adjustment for differences in the treatment group, age at randomization, sex, race/ethnicity, and baseline CVD risk factors (TC concentration, SBP or use of antihypertensive medication, smoking status, diagnosis of diabetes, and/or HDL-C concentration).



5.4.3 Conclusion

Prediabetes is categorised as an increase in an individual's risk for diabetes and other chronic diseases and excess mortality risk. HbA1c alone does not capture all of those with glucose dysregulation; insulin sensitivity and fasting analysis appear to be better correlated. In addition, it has been observed that changes in glucose regulation may take place up to 18 years in advance of any diagnosis.

Regression from a prediabetic state is also associated with a reduction in CVD risk overall. The literature review provides evidence that prediabetes is not only a precursor for diabetes but also associated with excess morbidity and mortality risk in and of itself.

5.5 COVID-19 Infection in People with Diabetes

It is a fact that people with diabetes are at increased risk of infections including influenza and related complications such as secondary bacterial pneumonia. People with diabetes have impaired immune-response to infection both in relation to cytokine profile and to changes in immune-responses including T-cell and macrophage activation. Poor glycaemic control impairs several aspects of the immune response to viral infection and to the potential bacterial secondary infection in the lungs.

Many patients with type 2 diabetes are obese and obesity is also a risk factor for severe infection. More specifically, abdominal obesity is associated with a higher risk due to the chronic, low-grade inflammatory state induced by abdominal adiposity. In addition, mechanical respiratory problems with reduced ventilation of the basal lung sections increase the risk of pneumonia.

Plasma glucose levels and diabetes are found to be independent predictors for mortality and morbidity in patients with SARS; potential mechanisms include 1) higher affinity cellular binding and efficient virus entry, 2) decreased viral clearance, 3) diminished T cell function, 4) increased susceptibility to hyperinflammation and cytokine storm syndrome, and 5) presence of CVD (Figure 18).

Figure 18: Putative mechanisms contributing to increased susceptibility for coronavirus disease (COVID-19) in patients with diabetes mellitus (DM)

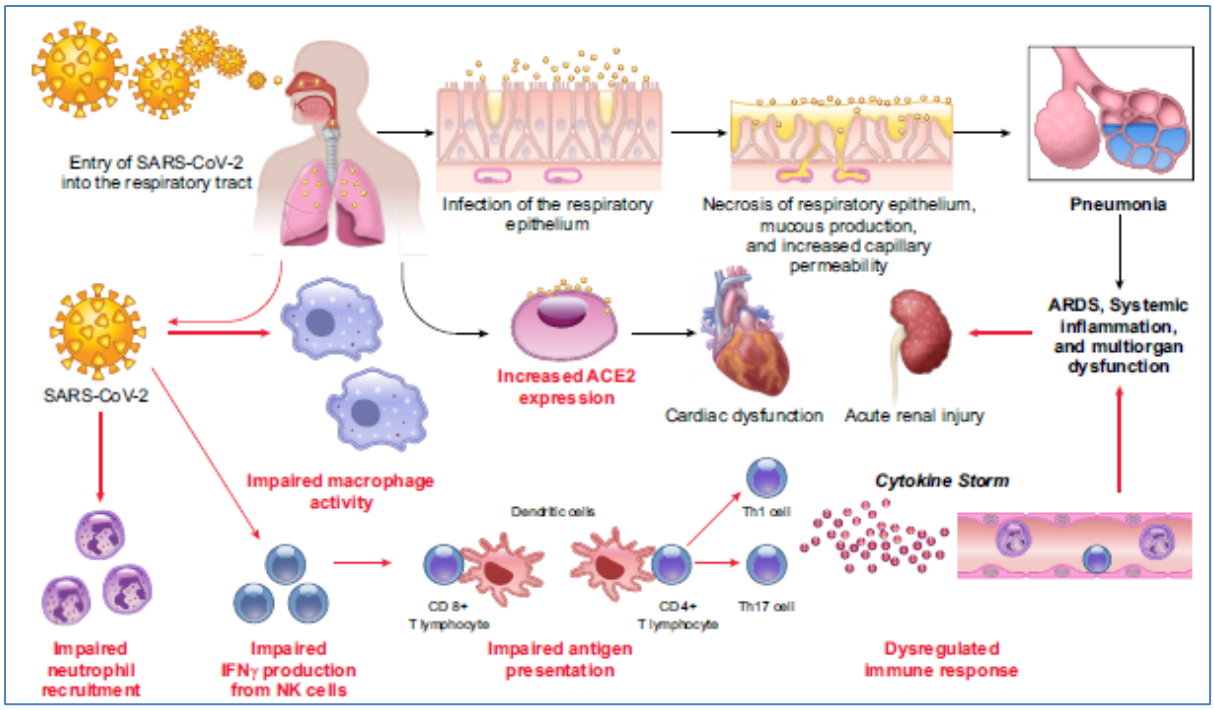


Figure 18. Following aerosolized uptake of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), invasion of the respiratory epithelium and other target cells by SARS-CoV-2 involves binding to cell surface angiotensin-converting enzyme 2 (ACE2). Increased expression of ACE2 may favour more efficient cell binding and entry into cells. Early recruitment and function of neutrophils and macrophages are impaired in DM. Delay in the initiation of adaptive immunity and dysregulation of the cytokine response in DM may lead to the initiation of the cytokine storm.

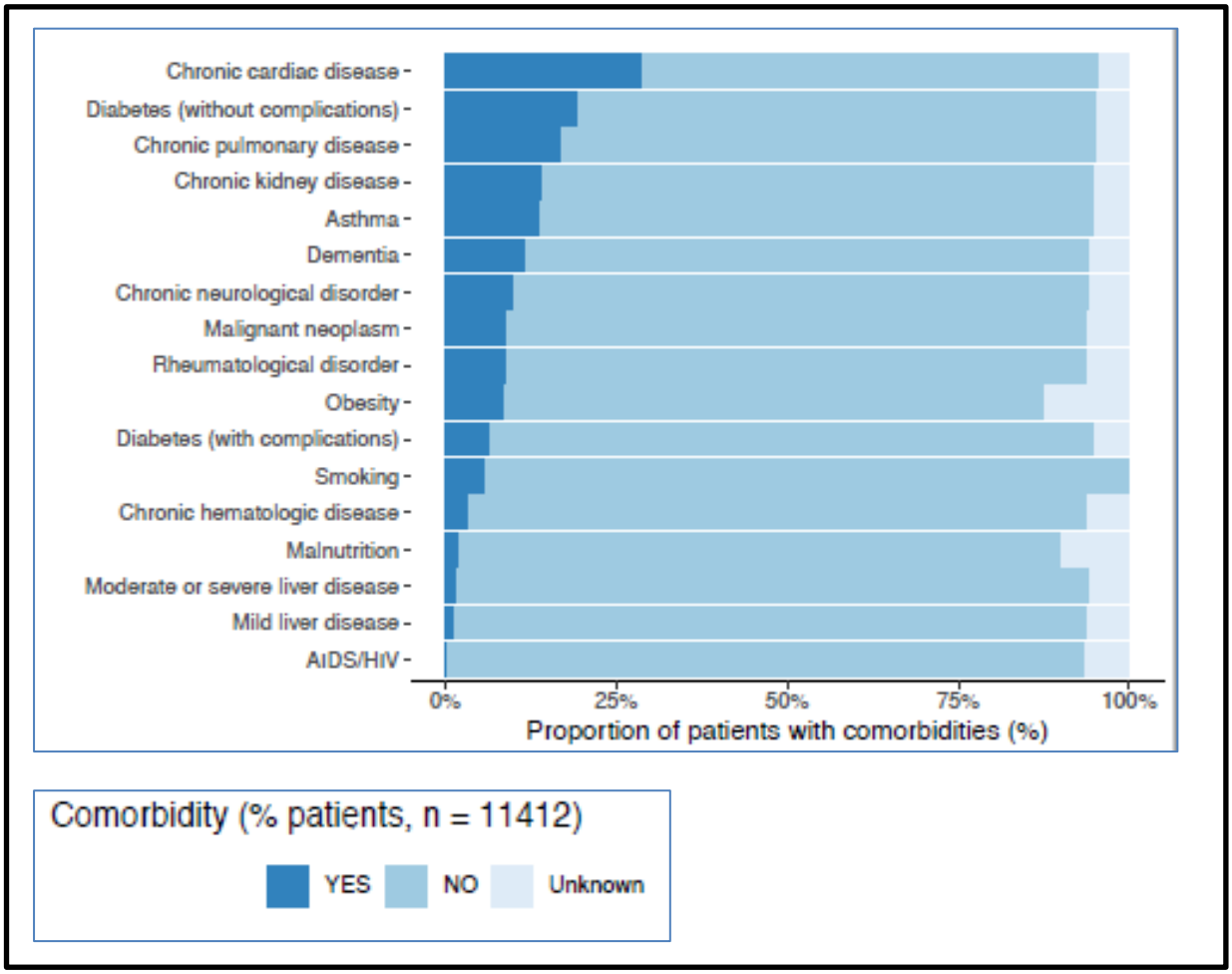
Several studies have identified that those with diabetes appear to be at greater risk of severe symptoms and death from COVID-19 (Kumar et al., 2020)

5.5.1 Hospitalised patients

One prospective observational cohort study with rapid data gathering and near real-time analysis, used a pre-approved questionnaire adopted by the World Health Organisation (WHO), to characterize the clinical features of patients with severe COVID-19 in the UK (Docherty et al., 2020).

In this study, 19% of those hospitalised with COVID-19 had uncomplicated diabetes (Figure 19).

Figure 19: Percentage of comorbidities



In addition, the ICNARC audit[6] (ICNARC, 2020)has identified that those with a high BMI are over-represented in ICU compared to general viral pneumonia patients. (Table 14 and Figure 20)

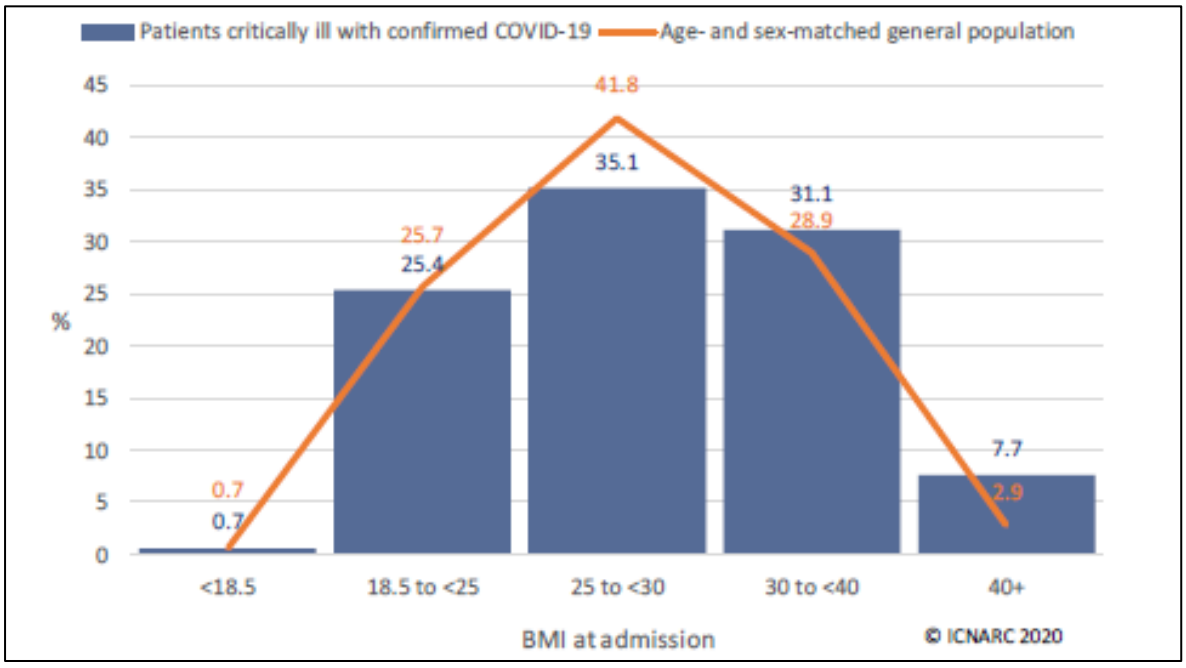
[6] ICNARC = the Intensive Care National Audit & Research Centre

Table 14: Patient characteristics: demographics

Demographics	Patients with confirmed COVID-19 and 24h data (N=9026)	Patients with viral pneumonia (non-COVID-19), 2017-19 (N=5782)
Age at admission (years) [N=9021]		
Mean (SD)	58.6 (12.5)	58.0 (17.4)
Median (IQR)	60 (51, 67)	61 (48, 71)
Sex, n (%) [N=9022]		
Female	2619 (29.0)	2641 (45.7)
Male	6403 (71.0)	3141 (54.3)
Currently or recently pregnant, n (% of females aged 16-49) [N=625]		
Currently pregnant	23 (3.7)	56 (7.4)
Recently pregnant (within 6 weeks)	34 (5.4)	29 (3.8)
Not known to be pregnant	568 (90.9)	674 (88.8)
Ethnicity, n (%) [N=8185]		
White	5468 (66.8)	4951 (88.4)
Mixed	138 (1.7)	52 (0.9)
Asian	1245 (15.2)	325 (5.8)
Black	797 (9.7)	155 (2.8)
Other	537 (6.6)	117 (2.1)
Index of Multiple Deprivation (IMD) quintile *, n (%) [N=8857]		
1 (least deprived)	1303 (14.7)	873 (15.3)
2	1442 (16.3)	999 (17.5)
3	1730 (19.5)	1115 (19.5)
4	2172 (24.5)	1232 (21.6)
5 (most deprived)	2210 (25.0)	1489 (26.1)
Body mass index *, n (%) [N=8344]		
<18.5	56 (0.7)	310 (5.5)
18.5-<25	2118 (25.4)	1933 (34.2)
25-<30	2932 (35.1)	1691 (29.9)
30-<40	2595 (31.1)	1330 (23.5)
40+	643 (7.7)	394 (7.0)

* Please see Definitions on page 34.

Figure 20: BMI distribution of patients critically ill with confirmed COVID-19



And in this large multi-variate analysis, (Williamson et al., 2021), risk of death for those with diabetes hospitalised with COVID-19 was found to be increased vs. those without diabetes (Table 14).

Table 15: Hazard Ratios (HRs) and 95% confidence intervals (CI) for in-hospital COVID-19 death

	CPNS Death HR (95% CI)	
	Age-sex adj	Fully adj
Diabetes (vs none)*3		
Controlled (HbA1c<58 mmol/mol)	2.02 (1.89-2.16)	1.50 (1.40-1.60)
Uncontrolled (HbA1c>=58 mmol/mol)	3.61 (3.34-3.90)	2.36 (2.18-2.56)
No recent HbA1c measure	2.35 (2.04-2.70)	1.87 (1.63-2.16)

5.5.2 Diabetes is a risk factor for the progression and prognosis of COVID-19

Analysis of the demographic data, medical history, symptoms and signs, laboratory findings, chest computed tomography (CT), and treatment measures in 174 consecutive patients confirmed with COVID-19 is presented here (Guo et al., 2020). This provides context as to why people with diabetes are at greater risk of severe symptoms and mortality from COVID-19.

Patients were divided into diabetes and non-diabetes groups according to their medical history. Furthermore, CT imaging scores were used to quantify the pathological changes in COVID-19 patients. The values were obtained by two physicians, who were blinded to patients' clinical data, using an introduced scoring system described below (Table 16).

Table 16: CT imaging scores

Number	Performance	Score
1	Unilateral patchy shadows or ground-glass opacity	5
2	Bilateral patchy shadows or ground-glass opacity	7
3	Diffuse changes for (1) or (2)	2
4	Unilateral solid shadow, strip shadow	2
5	Bilateral solid shadow, strip shadow	4
6	Unilateral pleural effusion	2
7	Bilateral pleural effusion	4
8	Increased or enlarge mediastinal lymph nodes	1

The demographic and baseline characteristics of the patients are displayed in Table 17.

Table 17: Demographics and baseline characteristics of patients infected with SARS-CoV-2

	No. (%) Total (n = 174)	Non-diabetes (n = 137)	Diabetes (n = 37)	P-value[a]
Age, median (IQR), y	59 (49-67)	58 (47-66)	61 (55-69)	.054
Gender				
Male	76 (43.7)	56 (40.9)	20 (54.1)	.152
Female	98 (56.3)	81 (59.1)	17 (45.9)	
Comorbidities				
Hypertension	43(24.7)	33 (24.1)	10 (27)	.713
Cardiovascular disease	32(18.4)	20 (14.6)	12 (32.4)	.013
Malignancy	17 (4.6)	16 (11.7)	1(2.7)	.187
Pulmonary disease	14(9.7)	12 (8.7)	2 (5.4)	.745
Cerebrovascular disease	13 (7.5)	12 (8.7)	1 (2.7)	.373
Chronic kidney disease	13 (7.5)	12 (8.7)	1 (2.7)	.373
Chronic liver disease	8 (4.6)	8 (5.8)	0	.288
Immunodeficiency	4(2.3)	4(2.9)	0	.294
Hepatitis B infection	2(1.1)	2(1.5)	0	.461
Signs and symptoms				
Fever	136 (78.2)	114 (83.2)	22 (59.5)	.002
Highest temperature, °C				
<37.3	38 (21.8)	23 (16.8)	15 (40.5)	.002
37.3 to 38.0	36 (20.7)	28 (20.4)	8 (21.6)	.875
38.1 to 39.0	73 (42)	62 (45.3)	11 (29.7)	.089
>39.0	27 (15.5)	24 (17.5)	3 (8.1)	.161
Fatigue	47 (27)	36 (26.3)	11 (29.7)	.675
Chill	119 (68.4)	98 (71.5)	21 (56.8)	.086
Cough	56 (32.2)	48 (35)	8 (21.6)	.121
Pharyngalgia	9 (5.2)	8 (5.8)	1 (2.7)	.729
Dizziness	23 (13.2)	17 (12.4)	6 (16.2)	.739
Headache	12 (6.9)	10 (7.3)	2 (5.4)	.970
Chest tightness	45 (25.9)	40 (29.2)	5 (13.5)	.053
Chest pain	15 (8.6)	14 (10.2)	1 (2.7)	.265
Shortness of breath	42 (24.1)	37 (27)	5 (13.5)	.089
Myalgia	36 (20.7)	30 (21.9)	6 (16.2)	.449
Nausea and vomiting	17 (9.8)	12 (8.8)	5 (13.5)	.581
Diarrhoea	21 (12.1)	18 (13.1)	3 (8.1)	.583
Mortality	9 (5.2)	5 (3.6)	4 (10.8)	.185

[a]*P* values indicate differences between diabetes and non-diabetes patients. $P < .05$ was considered statistically significant.

Compared to patients without diabetes, patients with diabetes had more cardiovascular disease (32.4% vs 14.6%) and less fever (59.5% vs 83.2%), but had no significant differences in gender and age, as well as mortality.

Table 18 displays the comparison of laboratory parameters between diabetic and non-diabetic COVID-19 patients.

Table 18: Comparison of laboratory parameters between diabetic and non-diabetic COVID-19 patients

		Median (IQR)			
	Normal range	Total (n = 174)	Non-diabetes (n = 137)	Diabetes (n = 37)	*P*-value[a]
HBDH (U/L)	72 to 182	190 (146-263)	190 (143.5-251.5)	210 (177-480)	.13
ALT (U/L)	5 to 35	26 (21-37)	25 (17-42)	28 (21-34)	.2
LDH (U/L)	109 to 245	248 (188-362)	241 (187-372.3)	252 (174.5-292.5)	.76
GGT (U/L)	11 to 50	25 (14-51.3)	24 (14-45)	32 (17.5-52)	.19
Lymphocytes ($\times 10^9$/L)	1.1 to 3.2	0.96 (0.7-1.3)	0.97 (0.74-1.3)	0.86 (0.5-1.3)	.04
Neutrophils ($\times 10^9$/L)	1.8 to 6.3	2.7 (1.8-4.6)	2.5 (1.6-3.7)	4.1 (2.8-6.9)	<.01
Red blood cells ($\times 10^{12}$/L)	3.8 to 5.1	4.14 (3.8-4.4)	4.17 (3.8-4.5)	3.9 (3.5-4.2)	<.01
Haemoglobin (g/dL)	115 to 150	124 (115-135)	127 (117-136)	117 (105-123.5)	<.01
C-reactive protein (mg/L)	<8	17.7 (7.34-51.8)	16.3 (7.17-43.9)	32.8 (11.3-93)	.06
Serum ferritin (ng/ml)	21.8 to 275	375.9 (169.5-746.9)	372.6 (185.8-685.8)	594.4 (164-1146.2)	.15
ESR (mm/h)	<15	28 (13-59)	23 (10-49)	67 (47.5-81)	<.01
IL-6 (pg/ml)	0.1 to 2.9	11.75 (5.1-28.2)	11.16 (4.5-25)	18.3 (7.3-37.6)	.07
D-dimer (μg/L)	<0.5	0.67 (0.3-1.4)	0.54 (0.25-1.1)	1.15 (0.83-2.11)	<.01
FIB (g/L)	2.0 to 4.0	4.78 (3.8-5.8)	4.58 (3.7-5.6)	5.1 (4.6-6.3)	.27

Abbreviations: ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; ESR, erythrocyte sedimentation rate; FIB, fibrinogen; GGT, γ-glutamyltransferase; HBDH, α-hydroxybutyrate dehydrogenase; IQR, interquartile range; LDH, lactic dehydrogenase.
[a]P values indicate differences between diabetes and non-diabetes patients. *P* < .05 was considered statistically significant.

This analysis suggests that serum levels of inflammation-related biomarkers such as IL-6, C-reactive protein, serum ferritin and coagulation index, D-dimer, were significantly higher (P < .01) in diabetic patients compared with those without, suggesting that patients with diabetes are more susceptible to an inflammatory storm eventually leading to rapid deterioration of COVID-19. In addition, the absolute count of lymphocytes, red blood cells, and Hb levels was significantly lower in the diabetes group compared to the non-diabetes group.

The representative chest CT imaging of patients with or without diabetes was compared, and the latter showed more severe pathological changes than the former (Figure 21 A). Furthermore, the severity of pathological changes was evaluated by the quantifiable score system described before. It was found that the diabetes group presented a higher CT imaging score compared with the non-diabetes group (Figure 21 B).

Figure 21: CT results of the patients with diabetes and patients without diabetes

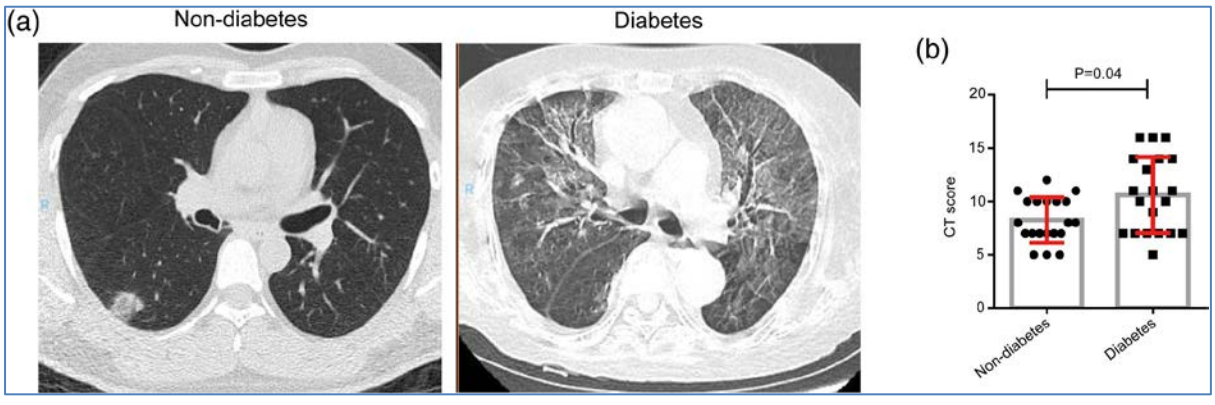


Figure 21

A. The representative CT images of the patients with diabetes and patients without diabetes
B. B, The CT score of the patients with diabetes and patients without diabetes. P < .05 was considered statistically significant. CT, computed tomography

5.5.3 Conclusion

In summary whether interference from other comorbidities is present or not, it was found that SARS-CoV-2 pneumonia patients with diabetes are more severe than those without diabetes evaluating from organ damage, inflammatory factors or hypercoagulability and are more likely to progress into a worse prognosis.

6 Global Underwriting survey

6.1 Prevalence of diabetes in countries covered in the global survey

Globally, more than 1 in 10 adults are now living with diabetes (type 1 and type 2). The global prevalence of diabetes is estimated at around 537 million adults aged 20-79 worldwide (10.5% of all adults in this age group) have diabetes, which has more than tripled, from an estimate of 151 million (4.6% of the global population) in 2000 (Webber, 2013). According to the World Health Organization, prevalence has been rising more rapidly in low-to-middle income countries (WHO, 2021)

Regions with the highest prevalence of diabetes (over 9%) currently include the Middle East and North Africa, North America and Caribbean, South and Central America and South-East Asia (Table 19). In terms of countries covered in our global survey, the United Kingdom and Ireland have a lower prevalence in 2021 than Malaysia, Singapore, Indonesia, Mainland China, and Hong Kong (Table 20).

Table 19: Age-adjusted comparative prevalence of diabetes, %, by region and year

Region	2011	2021	2030	2045
Africa	4.5	5.3	5.5	5.6
Europe	6.7	7	8	8.7
The Middle East and North Africa	11	18.1	19.6	20.4
North America and the Caribbean	10.7	11.9	13.3	14.2
South and Central America	9.2	8.2	9.2	9.9
South-East Asia	9.2	10	10.9	11.3
Western Pacific	8.3	9.9	10.9	11.5

Source: https://diabetesatlas.org/data/en/indicators/2/

Table 20: Age-adjusted comparative prevalence of diabetes, %, by countries that participated in survey and year

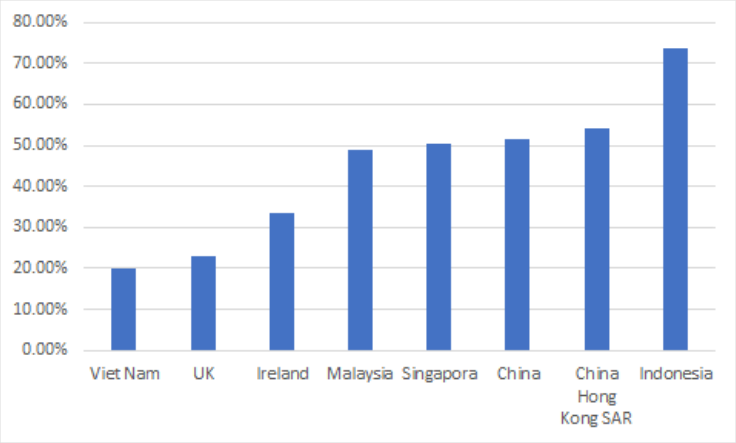
Country	2011	2021	2030	2045
United Kingdom	5.2	6.3	7	7.5
Ireland	5.2	3	3.6	3.9
Malaysia	12.1	19	18.9	19.6
Vietnam	3.2	6.1	6.7	7.1
Singapore	9.5	11.6	13.3	14.3
Indonesia	5.1	10.6	11.3	11.7
China, Hong Kong SAR	7.6	7.8	9.4	10.4
China	8.8	10.6	11.8	12.5

Source: https://diabetesatlas.org/data/en/indicators/2/

It is estimated that 44% of adults living with diabetes (240 million people) are undiagnosed and almost 90% of these people come from lower to middle-income countries. There are large regional variations in identifying undiagnosed diabetes due to healthcare resources and access to healthcare services. It is important for people with diabetes to be diagnosed as early as possible as this will help prevent diabetes complications and avoid premature early death (Webber, 2013).

There is significant variation between countries relating to the proportion of people living with diabetes that are unaware of their condition (Figure 22).

Figure 22: Proportion of people with undiagnosed diabetes



Source: (Webber, 2013)

A further consideration is to understand the global prevalence of people at risk of developing diabetes. Currently, there is no global medical consensus on the definition of "prediabetes", and there are several different definitions depending on the clinical organisation (Keywords and Section 5.4).

In 2021, it was estimated that 541 million adults, or 10.6% of adults worldwide, have impaired glucose tolerance (IGT, Keywords); and 319 million adults, or 6.2% of the global adult population, have impaired fasting glucose (IFG, Keywords). Furthermore, the prevalence estimates are expected to increase in the future (Webber, 2013).

The trends in the prevalence of diabetes increasing over time (Table 19 and Table 20), with a significant proportion of undiagnosed diabetes and people at risk of developing diabetes (prediabetes), points to major challenges for the future risk of diabetes across the globe.

According to the WHO, Diabetes mellitus is in the top 10 leading causes of death in 2019 and it is increasing as a cause of death over time (WHO, 2020). Diabetes is also a leading and increasing cause of disability, along with obesity that is linked to severe health problems, like heart disease, stroke, kidney failure, leg amputation, vision loss and nerve damage (WHO, 2016).

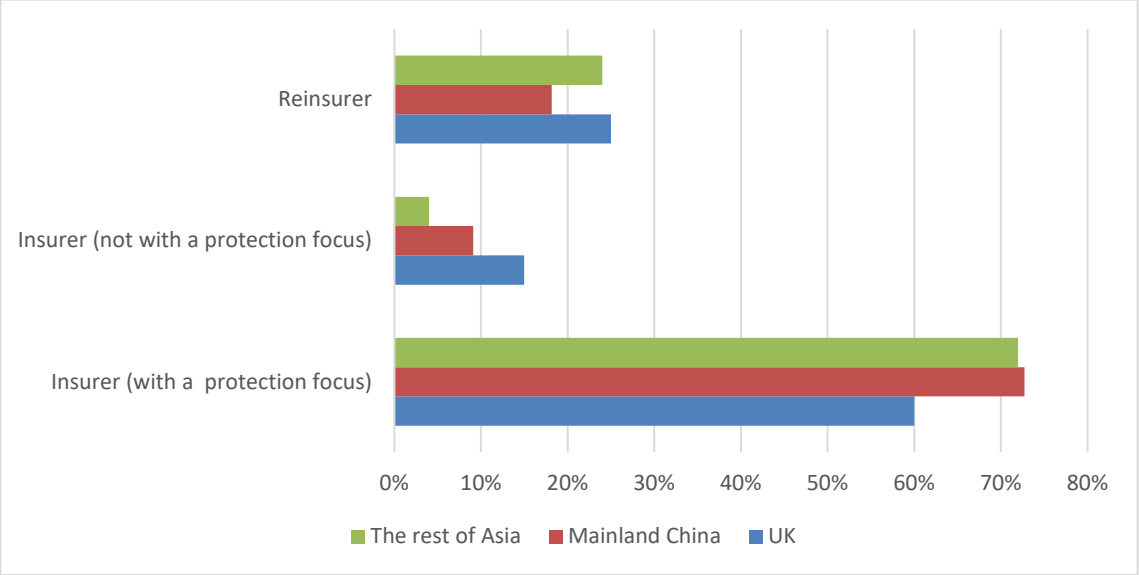
6.2 Regions covered by the global underwriting survey

An important aim of this research was to widen the geographical scope given that diabetes is a global condition, and insights could be gained by comparing how different countries deal with insuring people

with diabetes. Given this aim, the underwriting survey covered the UK, Mainland China, and the rest of Asia[7].

The survey conducted over three regions received a good number of participants across a broad range of firms (Section 4). In the UK, 20 insurers participated, 55 in Mainland China and 25 in the rest of Asia. We asked direct insurers and reinsurers if they were protection-focused or not. Most firms that participated are protection-focused (Figure 23). The firms that were not focused on protection based in the UK included those that write longevity business (enhanced annuities) and in the Asian region include health insurers predominately but also includes P&C firms.

Figure 23: What type of insurer do you work for?



Source: IFoA Global Underwriting Survey

There are differences across the regions in terms of the likelihood of being offered protection coverage if you are a person with type 1 or type 2 diabetes (Figure 24 and Figure 25).

The survey asked the participants how likely they would offer people with type 1 diabetes an insurance product. The outcomes across the three regions demonstrated wide availability of life cover (mortality products), but with lower accessibility to Critical Illness or Disability Income (Figure 24). A similar outcome was observed for type 2 diabetes, however, with a slight increase in the availability of critical illness and disability income products (Figure 25).

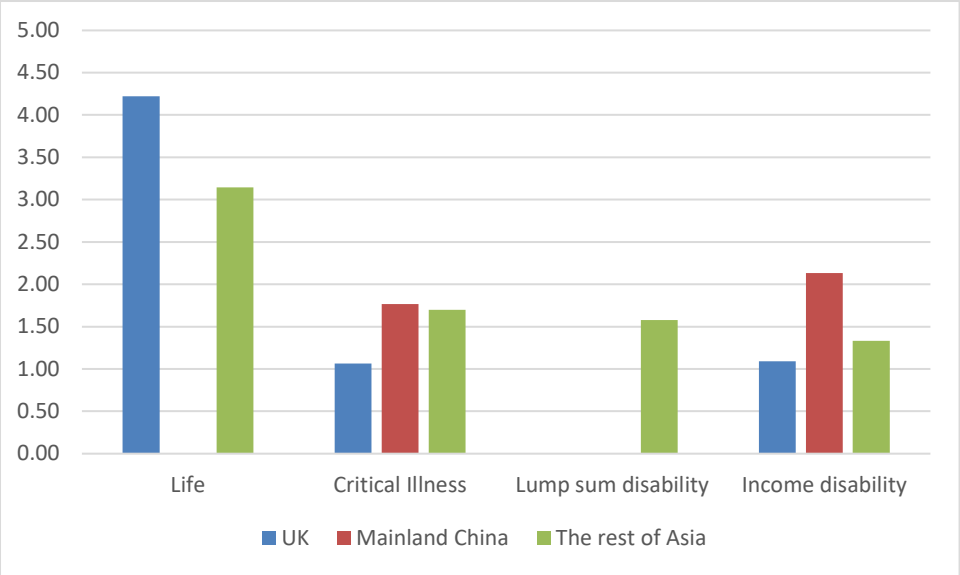
Based on this survey, the UK has lower accessibility for people with diabetes for Critical Illness and Income Protection (Disability Income) compared to Asia. Considering the likelihood scores 1 (very unlikely) to 5 (very likely) for these products in the UK, on average the score is approximately 1.5 for type 2 as opposed to type 1, which is much close to 1 (very unlikely).

Lump-sum disability is offered as a separate product in some markets. For example, TPD (Total Permanent Disability) is common in the rest of Asia but not in the UK and Mainland China.

[7] DWP conducted three surveys for companies based in the UK and Ireland, Mainland China and the rest of Asia, due to logistical reasons. For participation in UK and Ireland, the majority are in the UK. The survey in Mainland China was translated into Chinese to encourage higher participation. For simplicity, this paper refers to “The UK”, “Mainland China” and "the rest of Asia”.

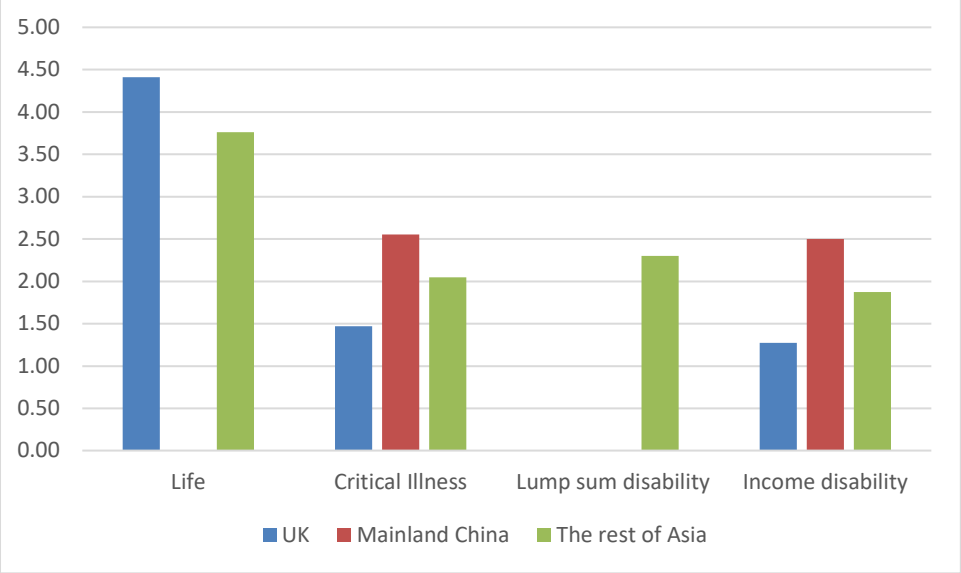
The differences between the regions in terms of accessibility could, in part, be explained by how the public healthcare system is funded. In the UK, the public healthcare is funded publicly, whereas, in Asia, many countries have a high proportion of care funded privately. Individuals with diabetes in Asia may have to self-fund a large proportion of their medical costs, therefore triggering the need for such coverage from a Critical Illness and Disability Income perspective, which is not necessarily the case in the UK. As there is a greater need for insurance in Asia, this could explain why this market is more developed compared to the UK in terms of accessibility.

Figure 24: How likely would it be that you would offer the following benefits to an applicant with type 1 diabetes (1 is very unlikely and 5 very likely)?



Source: IFoA Global Underwriting Survey

Figure 25: How likely would it be that you would offer the following benefits to an applicant with type 2 diabetes (1 is very unlikely and 5 very likely)?



Source: IFoA Global Underwriting Survey

6.3 Market overview of countries covered in the survey

6.3.1 Overview of UK protection market

The UK life market sells long-term life business called Protection, predominantly through an intermediary market. The key products in the UK Protection market include Term, Critical Illness and Income Protection. The market for products targeting people with diabetes is at an early stage and niche.

People with diabetes (type 1 and 2) can access Term cover (including Terminal Illness). However, a limited number of products are targeted specifically at people with diabetes (Table 21). The products on offer incentivise the customer by adjusting the premium level to reward good control of their diabetes. The feature to control diabetes through adjusting the premium level (aka continuous underwriting) is a UK market feature and is not common in Asia.

A key measure used for good control of diabetes is HbA1c (Keywords) which measures the average blood (sugar) levels for the last 3 months. A person with diabetes with good control will have an HbA1c measure at 48mmol/mol or 6.5% or below.

Table 21: Examples of the diabetes propositions in the UK market

	Vitality	The Exeter	Royal London
Line of business	Life	Life	Life
Product name	Wellness Optimiser	Managed Life	Diabetes Life Cover
Issue age	16	18	18
Channel	Intermediary	Intermediary	Intermediary
Target market	Healthy people	Type 2 Diabetes High BMI customers	Type 1 and Type 2 diabetes
Underwriting	Full	Full	Full
Insured events	Death/Terminal Illness	Death/Terminal Illness	Death/Terminal Illness
Type of benefit	Lump sum	Lump sum	Lump sum
Additional benefit	Rewards Program Cash back	n/a	Helping Hand Service – access to specialist diabetes nurse for advice
Premium structure	Level Adjustable based on blood sugar blood pressure BMI cholesterol measure	Level Adjustable based on blood test results (up to 35% reduction)	Level, adjustable based on blood test results (up to 40% reduction
Monitoring method	Customer submitted Pharmacist health check	Customer submitted	Customer submitted

Source: Diabetes WP research

These types of products for people with diabetes are niche and sales to date have met with limited success.

6.3.2 Overview of UK enhanced annuity market

In the UK, there is a longevity market for annuity products, where a product known as “enhanced annuity” or “impaired annuity”, or “medically underwritten annuity”, has emerged since 1990s. It is aimed to provide people with a major health condition(s) a much higher annuity income because such people are expected to have a shorter life expectancy than their healthier peers.

According to figures released by the industry, over half of the customers (52% in 2017) and in the first two quarters of 2018, enhanced annuities made up 41% of all sales. However, many more individuals may qualify for an enhanced annuity should they shop around at retirement. Currently, only half of the customers purchase annuities from a new provider (Association of British Insurers, 2019).

Diabetes (both type 1 and 2) is one of the main conditions which qualifies for an enhanced annuity, together with other conditions like cancer or heart disease, as well as lifestyle choices such as smoking. It is therefore important for the industry to understand the mortality impact of diabetes at older ages.

6.3.3 Mainland China

In Mainland China, people with diabetes can purchase a range of products: whole life insurance, term life insurance, savings, and limited medical and Critical Illness products. China has around 141 million people in 2021 with diabetes (the total population of China estimate 1,413 million in 2021) based on the IDF Diabetes Atlas (Webber, 2013). It has created an innovative environment for insurers to launch diabetes focused products (Table 22).

This market started about 10 years ago when some insurance companies launched health insurance products that targeted people with type 2 diabetes. These products provided a fixed lump benefit on diagnosis of one of four diabetes complications (including sequelae of stroke, amputation, end-stage kidney disease and blindness). However, the sales of these initial products had limited success. In recent years, we have seen a range of products from medical to Critical Illness being launched to provide protection for people with diabetes or prediabetes.

Table 22: Example of the diabetes propositions in the Mainland China market

	Zhong An	Taikang	Ping An Life
Line of business	Medical	Accelerated Critical Illness	Whole of Life Accelerated Critical Illness Plus additional one year diabetes cover (guaranteed to renew for 5 years)
Product name	An-Wen-E-Sheng Medical Insurance Product	Tian Mi Ren Sheng (A) Specific CI	Tang Bao Bao
Issue age / Term	18-55	30-65 / Term 5, 10 or 20 years.	18-55
Channel	Online	Intermediary	Online
Target market	Type 2 or essential hypertension	Type 2 diabetes	Type 2 diabetes and prediabetes
Underwriting	Simplified	Full	Simplified

Insured events	Incidence of treatment	Incidence of Critical Illness or death	Incidence of Critical Illness or death
Type of benefit	Hospitalisation, specialised outpatient, annual deductibles, pay-out ratio 90% (50% without using social care reimbursement)	Sum Assured paid on the diagnosis of one of 4 diabetes complications: sequelae stroke; Amputation; end stage kidney disease; and blindness.	Sum assured 500k max for CI; 150k for additional diabetes cover. Whole of Life CI 1. Death benefit full SA 2. CI benefit (100 conditions) full SA 3. Minor CI benefits (50 conditions) 20% of SA up to 3 times One year diabetes cover 30% of SA on diagnosis of 1 of 5 diabetes complications.
Additional benefit	n/a	n/a	Glucose management service
Premium structure	One year, renewable till age 80	Guaranteed level	Guaranteed level
Monitoring method	Health check	Health check	Health check

Source: Diabetes WP research

Notes on table

- Mid-End Medical Insurance Product (Zhong An): these types of products typically provide general medical benefits to the insured which covers hospitalization fee for bed, meals, and care. Special outpatient benefit covers treatment cost for cancer, post organ transplantation. Some products also offer rider benefits include lump sum payment for diabetes complications and Hospitalization Income for diabetes complications.
- Specific CI Product (Taikang): benefits are simple and only covers diagnosis of one of a few diabetes complications where a lump sum benefit is paid. There are a limited number of diabetes related Critical Illness products available on the market. It is a normal accelerated Critical Illness that targets type 2 diabetes patients and provides additional cover for diabetes complications. For the specific product from Taikang, it also provides glucose management services.
- Whole of Life CI Product (Ping An Life): Over last 10 years' development, Diabetes related products are still not the mainstream product and there are only about 30 products available (small compared with more than 1000 CI products available on the market).

The volumes have also been disappointing to date and this is down to mainly two reasons:

The first reason is diabetes related products target sub-standard lives, which has a higher risk and is more complex risk compared to healthy lives where we have more data for pricing, and we therefore understand the risk better.

To control the risk, we need to embed the health management services into the product, as diabetes patients with healthier lifestyles or better control of their glucose levels have an improved morbidity and mortality risk. Also, the demands of diabetes patients are more complex than an otherwise healthy life, they not only need protection from Illness, but they also have a demand for their glucose management and medical services both inside and outside hospital.

The second reason is related to sales. The agency or online channel are currently unable to reach a mass population of people with diabetes, which is leading to lower-than-expected sales volume. This means a more innovative sales approach is required to improve sales e.g., insurance companies may need to collaborate with diabetes patients' club/groups. Alternatively, the insurance company may need to cooperate with third parties that sell glucose meter or other services.

While the sales of Critical Illness products have hit a plateau in China, many insurance companies have started to consider developing sub-standard life products, which is also encouraged by regulators, and we expect to see a rapid development of new diabetes products in the future.

6.3.4 The rest of Asia (excluding Mainland China)

The rest of Asia's insurance markets sell products covering a more comprehensive range of risks, including mortality, Critical Illness, Hospital Cash and Medical Reimbursement. The market for products targeting people with diabetes has been growing over recent years, with protection offerings ranging from mortality to Critical Illnesses to Medical Reimbursements (Table 23).

Unlike the UK market, the premium structure is less complicated. The products mainly cover Type 2 diabetes only.

Table 23: Examples of the diabetes propositions in the rest of Asia (excluding Mainland China) market

	AIA Singapore	AXA Hong Kong	PRUDENTIAL Indonesia
Line of business	Life	Life	Life
Product name	AIA Diabetic Care	Managed Life	Diabetes Life Cover
Issue age	30-65	18+	31-65
Channel	Intermediary	Intermediary	Intermediary
Target market	Type 2 and prediabetes	Type 2 High Blood pressure, High Cholesterol, and High BMI	Type 2 diabetes
Underwriting	Simplified	Full	Full
Insured events	Critical Illness that is relevant to DM patients	Critical Illness / Medical Insurance	Death / Medical Insurance
Type of benefit	Lump sum	Lump sum / Medical Reimbursement	Lump sum / Medical Reimbursement
Additional benefit	Reward program	Health management program	n/a

Premium structure	Level	One-off 15% premium rebate on original premiums after completion of a 12-month program	Charged under ILP structure
Monitoring method	Customer submitted	Nurse consultation	n/a

Source: Diabetes WP research

The market for this segment is still niche, as the insurers and distributors predominately focused on offering insurance protection to the healthy lives segment. Despite this, we observed higher interest in this segment over recent years, as some companies started to pilot product offerings across different types of risks for this customer segment. In addition, more countries in Asia started campaigns to raise awareness of managing diabetes in recent years, such as: "World Diabetes Day" in multiple Asian countries; "War on Diabetes" in Singapore; and "For your sweetheart Campaign" in Malaysia. As a result, we expect the interest in offering protection to people with diabetes will continue to increase.

6.4 Rating/risk factors used by industry and the medical community

6.4.1 Overview

The underwriting survey asked insurers/reinsurers globally what rating factors they use to assess type 1 and type 2 (section 6.5.4). It is useful to consider a high-level view of the rating factors used by the industry and how this compares against the risk factors used by the medical community (Table 24).

Rating factors are risk factors or proxies for risk factors to determine the premium rate, whereas risk factors are the factors that influence the intensity of the risk. In practice, some risk factors might not be easy to measure or may not be a material driver of the risk.

The insurance/reinsurance industry uses rating factors for people who have diabetes that align well with the medical community except for lifestyle choices like inactivity/exercise and diet (Table 24). The key risk factors used by the medical community to improve the public's health is around lifestyle choices. Exercise and diet are two areas that are a challenge to measure currently. However, new technologies are making these lifestyle habits more measurable, which may lead to innovation in the insurance industry to collect this type of information and nudge customer behaviour towards healthier lifestyles.

Table 24: Protection business type 1 and 2, mortality risk

Ratings used by the industry	Risks factors used by the medical community
- Age - Gender - Duration from inception - BMI - Smoker status - Product – Life, Critical Illness and Income Protection - HbA1c - Blood pressure (diastolic/systolic) - Cholesterol (HDL ratio)	Public health considers the following as key risk factors in reducing diabetic complications and premature death: - Inactivity/Exercise - Weight management - Unhealthy diet/food composition - smoking Results from a UK National Diabetes Audit (NDA) multivariate analysis of mortality, 2017-2018 audit used the following risk factors: - Age - Ethnic group - Gender - BMI - Deprivation - Smoker status - HbA1c (mmol/mol) - Cholesterol

	- Occurrence of a complication Occurrence of complication includes: Angina, Myocardial Infarction, Heart Failure, Stroke, Major Amputation (above the ankle), minor Amputation (below the ankle), Renal replacement therapy (ESKD), DKA (for type 1 only)

Source: IFoA Global Underwriting Survey and National Diabetes Audit (NDA) – Report 2 Complications and Mortality, 2017-18 (NDA HQIP, 2019a)

Additional risk factors that increase the risk of type 1 or 2 diabetes is the occurrence of co-morbidities. They could also be used to understand the extent of how well the person with diabetes has controlled their glucose levels over time (Table 24).

6.4.2 How are rating factors applied?

We will consider briefly protection and longevity products and how an applicant's risk is accessed over time as their health changes.

Type 1 and type 2 diabetes are different types of diseases and should be treated separately. Type 1 diabetes is a genetic condition that often shows up early in life, and type 2 is mainly lifestyle-related and develops over time and usually later in life. The risk of type 2 occurring will depend on the risk factors for type 2 e.g., Age, BMI, smoker status, Blood pressure (diastolic/systolic), Cholesterol (HDL ratio).

6.4.2.1 Protection

Customers with diabetes that apply for a protection product will be underwritten at outset at the application stage. The underwriter will assess the risk of the applicant against a healthy life and will apply a loading to allow for additional risk. Most products are based on the customers health at outset; however, some products have introduced the concept of continuous underwriting where information is re-assessed in relation to modifiable risk factors over time (BMI, cholesterol, HbA1c, blood pressure).

To illustrate how a customer is underwritten at the point in time they apply for cover (from outset), we consider how a person's life changes health over-time through various health states (Figure 26). In this case, they would be underwritten as healthy up to age 42 and pre-diabetic from age 43 to 44 through being underwritten as a person with diabetes between the ages 45 and 48. From age 49, they would be underwritten as a person with diabetes and a co-morbidity myocardial infarction (MI) which would be considered a much high risk of death compared to just being an applicant with only diabetes.

Figure 26: Illustration of a customer timeline and how they will be underwritten for a term assurance product

Attributes\Year	1990	1991	…	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Age	21	22		41	42	43	44	45	46	47	48	49	50	51
Gender	M	M		M	M	M	M	M	M	M	M	M	M	M
Has diabetes	0	0		0	0	0	0	1	1	1	1	1	1	1
Has MI	0	0		0	0	0	0	0	0	0	0	1	1	1
BMI	27	27.5		28	28	29	30	31	30	29.5	29	30	28	27
HbA1c %	?	?		?	?	5.8	?	6.7	7	7.5	7.5	7.2	7	6.5
……						Prediabetes								
	Underwrite as healthy													
								Underwrite as diabetes						
												Underwrite as MI		

Source: Own figure

If a customer applying for a protection policy is healthy when underwritten, they will be classified as healthy throughout the duration of the policy even if they subsequently develop type 1 and 2 diabetes. A healthy live with no underlying co-morbidities at time of underwriting will be classified as a healthy life (no loading will apply).

Prediabetes is more of a challenge to underwrite as there are low levels of awareness and testing in the general population. If underwritten in the UK market, we would consider 6.0% <= HbA1c <= 6.4% as a prediabetes ("Sherwood Z," 2018). Many customers applying for protection may also be unaware of an underlying prediabetes condition as it tends to lack any specific symptoms. If a customer is more at risk of developing diabetes (e.g., prediabetes) then a loading may apply at outset to reflect the slightly higher risk of mortality/morbidity compared to a standard life, to reflect the 5-10% annual conversion to diabetes (Tabák et al., 2012b)

When a customer is diagnosed with diabetes type 1 or 2 but has no other serious co-morbidity, we will refer to them as a "healthy diabetic". In this case, they will have a higher risk of developing co-morbidities which will lead to an increased risk of a morbidity/mortality event compared a healthy life. Also, many customers with type 2 diabetes may have been unaware of their condition. A loading will apply to reflect the higher risk which will be higher in comparison to a person with prediabetes or a healthy life.

Finally, if a customer with diabetes has had an MI event, the underwriting will be based on a significant co-morbid risk between the diabetes and MI. This is likely to lead to a decline as a high likelihood of a future mortality/morbidity event compared to a healthy life.

Longevity

Diabetes is considered by annuity underwriters only when "enhanced" annuities from the UK market are involved. Similarly, for protection products, annuitants are only underwritten at the outset and the outcome will be dependent on the customers' health at that point in time.

The following table illustrates how an annuitant's life changes health over time going through various healthy states (Figure 29). In this case, they would be underwritten as healthy up to age 64 and as a diabetic between the ages 65 and 68. Although the customer has pre-diabetes between 63 and 64, they currently would not qualify for an enhanced annuity during those ages as pre-diabetes does not necessarily lead to type 2 diabetes and a subsequent reduction in life expectancy. From age 69, the customer has two major health conditions (e.g., diabetes and MI), both qualify for an enhanced annuity rate. In this case, the customer would be underwritten with the condition that is expected to give them the shortest life expectancy.

Figure 27: Illustration of a customer timeline and how then will be underwritten for an enhanced annuity product if they bought the product at various stages of their life

Attributes\Year	2000	2001	…	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Age	51	52		61	62	63	64	65	66	67	68	69	70	71
Gender	M	M		M	M	M	M	M	M	M	M	M	M	M
Has diabetes	0	0		0	0	0	0	1	1	1	1	1	1	1
Has MI	0	0		0	0	0	0	0	0	0	0	1	1	1
BMI	27	27.5		28	28	29	30	31	30	29.5	29	30	28	27
HbA1c %	?	?		?	?	5.8	?	6.7	7	7.5	7.5	7.2	7	6.5
……						Prediabetic								
	Underwrite as healthy													
								Underwrite as diabetes						
												Underwrite as the combination of conditions with shortest life expectancy		

Source: Own figure

From 2018 (red in Figure 29), if the customer had an MI a year ago, the mortality impact of that would far outweigh the mortality impact of diabetes, but we would still consider the interaction between the two. The customer with co-morbidities will get a higher rating than someone with just diabetes or just MI, depending on the interaction between the conditions.

6.5 Underwriting approach for people with diabetes

6.5.1 Risk Assessment in Diabetes Mellitus Applicants

Insurance risk assessment has over time become ever more sophisticated for a variety of reasons. Improved data sources have allowed insurers to understand and classify individual risks with better certainty. Alongside, more detailed studies that have better reflected additional risk factors have allowed insurers to explore more detailed risk assessment criteria. Underwriting guidance includes multiple individual risk factors to sub-divide the risk associated with an individual's diabetes to provide more individualised decisions from life and health insurers.

Numerous factors are used by insurers, often supported by reinsurers underwriting guidelines, to provide greater individual risk assessment using additional criteria. The extensive use of evidence-based research factors that contribute to higher or lower risk for an applicant with diabetes can be used based upon the approach being based on relevant actuarial or statistical data. The use of the factors within Table 24 reflects the potential differences in individual risk which insurers now use to provide a base for their risk assessment. We understand insurers continue to update their risk assessment processes based on the latest medical studies and evidence with the aim of providing insurance cover to an increasing pool of individuals.

The factors that are used with the risk assessment process may vary across different insurance markets, which may reflect their own risk appetite or the development and use of differing guidelines.

Factors that could be used may include the type of diabetes, with different expected ratings. The age, gender of the applicant and for how long the applicant has had diabetes are considered important factors and readily available information. How the applicant manages their diabetes may be obtained either from the applicant or confirmed by their diabetic clinic and attending physician. Usually, control is assessed by numerous blood glucose level tests, including HbA1c levels and their treatment alongside their adherence to this (section 6.4.2).

Complications to diabetes will affect the insurance risk assessment, including the existence of increased albuminuria or proteinuria in urinalysis, among many other established complications as well as the possible presence of cardiovascular risk factors.

6.5.2 Application form questions

Diabetes is an important focus for insurance risk assessment. However, the prognosis for those diagnosed with diabetes has improved over time. Such diagnoses will lead insurers to request further information from the applicant and/or the applicant's medical practitioner. The survey found that in Mainland China, 91% of insurers have a specific question regarding diabetes; in the UK this is 85% and much lower in the rest of Asia at 68%. The focus and questioning of applicants regarding diabetes is aimed at type 2. In the UK, all those UK insurers asking about diabetes referred to type 2. In Mainland China, the number of insurers asking about type 2 reduces from 91% (of insurers asking diabetes questions) to 87%; in the rest of Asia, it drops from 68% to 60%.

There are slightly more participants in the survey who refer in their proposal form questions to insurance applicants asking about 'whether they have abnormally raised blood sugar?'. The participants in Mainland China were 86% slightly lower than proportion with a diabetes question, which is also lower in the UK with 75%, but higher in the rest of Asia with 84%. It highlights that some insurers prefer to reference diabetes in relation to what they believe their insurance applicants may understand better by asking about raised blood sugar.

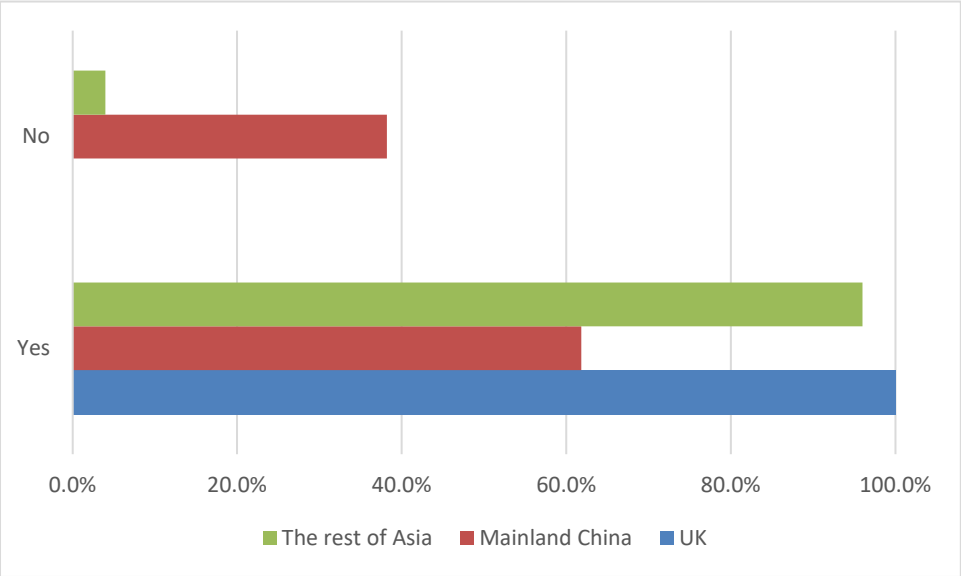
The number of participants asking a specific question of the applicant whether they have 'pre-diabetes' is considerably lower across all regions in the survey. Mainland China has a higher percentage of participants asking about prediabetes at 36%, with 30% in the UK and the lowest being in the rest of Asia at 24%.

The survey showed a different approach across the regions, with the majority asking applicants about diabetes or raised blood sugars; however, a much lower number of participants asked regarding pre-diabetes. It appears to be an interesting variation in questions regarding diabetes, as insurance guidelines often do specifically assess prediabetes or impaired glucose intolerance in the risk assessment process. Such applicants may be risk rated.

6.5.3 Guidelines in assessing diabetes in insurance applicants

There may have been a misunderstanding of this question about the use of specific diabetes guidelines in risk assessment for underwriting purposes. In the UK, all participants who answered this question indicated they have such specific guidelines. It is similar to the rest of Asia, with 96% of participants indicating they have specific guidelines. However, it was considerably lower for China with 62%. It may be a misunderstanding of the question set, as shown in Figure 30.

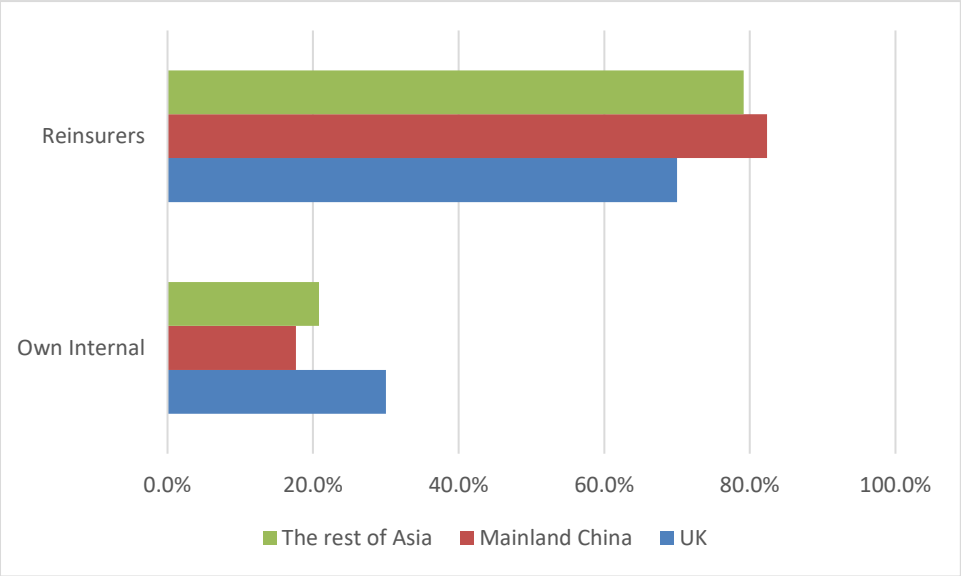
Figure 28: Specific risk assessment guidelines used for the underwriting of diabetics?



Source: IFoA Global Underwriting Survey

Of those who indicated they have specific guidelines, the survey found that most of these guidelines used are created by reinsurers and insurers rely on this expertise, as can be seen below in Figure 31.

Figure 29: Guidelines based upon your 'own' internal assessment of the risk, or do you use those provided by 'reinsurers'?

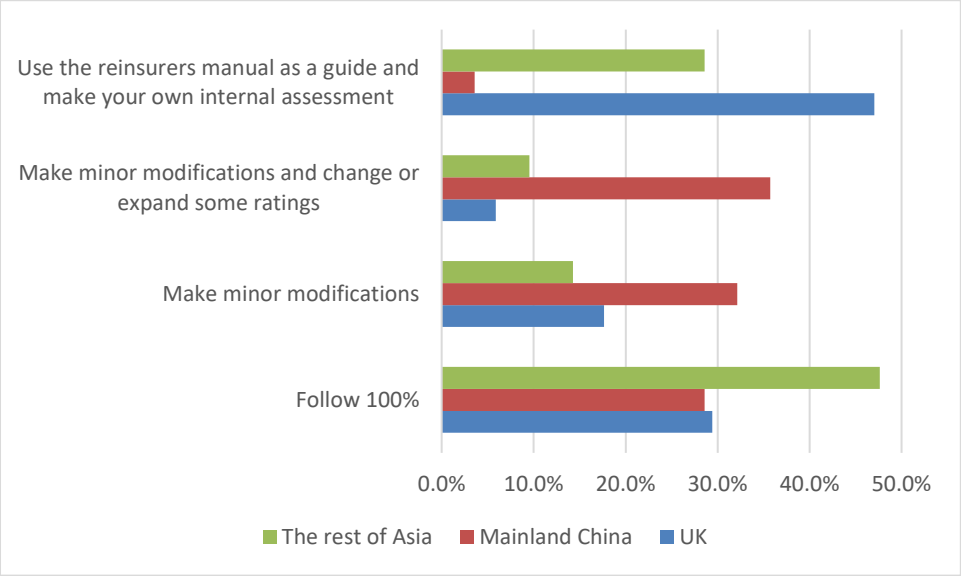


Source: IFoA Global Underwriting Survey

The survey found that in the UK, 30% of participants used their own guidelines, whilst 18% in Mainland China and the rest of Asia 21%. This shows a reliance on the diabetes guidelines produced by reinsurers, and this was particularly so for those who have guidance in China.

There is no universal approach to the use of reinsurer guidelines amongst the survey participants, and their use is widespread as in Figure 32. In the UK, almost half of participants use (47%) these as a guide, whilst in Mainland China, these are used, however with minor adjustment. The survey shows that in the rest of Asia reinsurer guidelines are more closely followed and adhered to with 48% of participants indicating these are thoroughly followed.

Figure 30: How do you use the reinsurer guidelines?



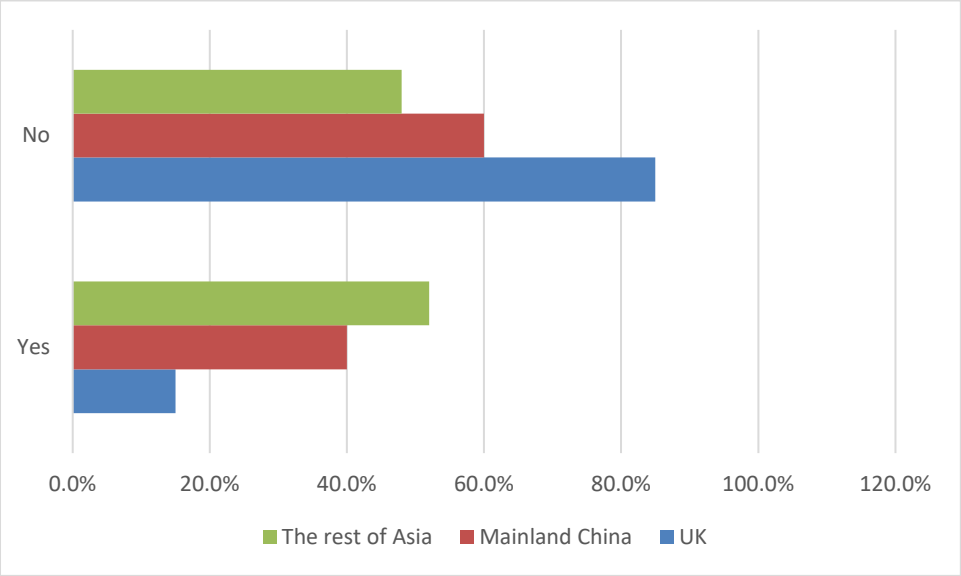
Source: IFoA Global Underwriting Survey

6.5.4 Diabetic risk factors used in risk assessment

Age is widely accepted as an important risk factor when assessing an applicant with diabetes risk. With all UK survey participants indicating its use in their underwriting approach, this is lower in the rest of Asia (88%) and Mainland China (84%).

There was a much lower observed use of applicant's gender in the risk assessment of diabetes, particularly shown in the UK, where only 15% of participants indicated the use of gender as opposed to a higher use in Mainland China with 40% use and even higher for the rest of Asia a slight majority do use this risk factor at 52%, as shown in Figure 33. It may reflect greater sensitivities on the use of gender created by the EU Gender Directive, even though guidance indicating its use would be acceptable in relation to the different health outcomes.

Figure 31: Do you use the applicant's gender in your risk assessment of diabetes?

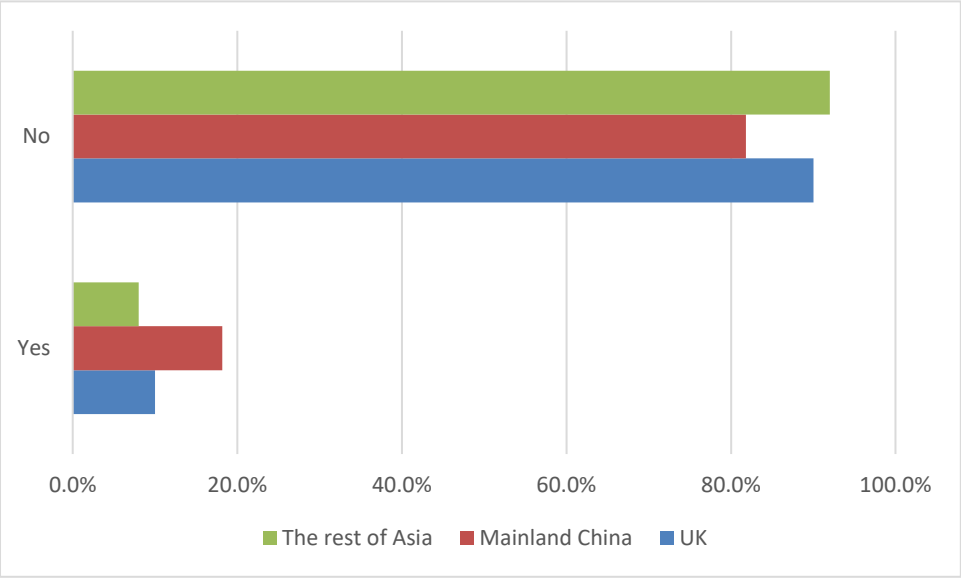


Source: IFoA Global Underwriting Survey

Insurers are increasingly looking to introduce new risk factors, where they use evidence to be relevant to the risk assessment. The use of physical activity is one of these newer factors, which are easy to collect and makes the information more accessible for applicants and insurers. Easier risk factors allow insurers to make decisions more quickly and allows insurance to be offered to more applicants and potentially more cheaply without expensive medical test or reports.

There is currently a low usage of physical activity in the risk assessment process for applicants with diabetes. This is a general low use of such attributes, although this may change in the future. The survey found that the use of physical activity is more significant in Mainland China (18%) but lower in the UK (10%) and the rest of Asia 8%, as shown in Figure 34.

Figure 32: Do you use the applicant's physical activity levels in your risk assessment?

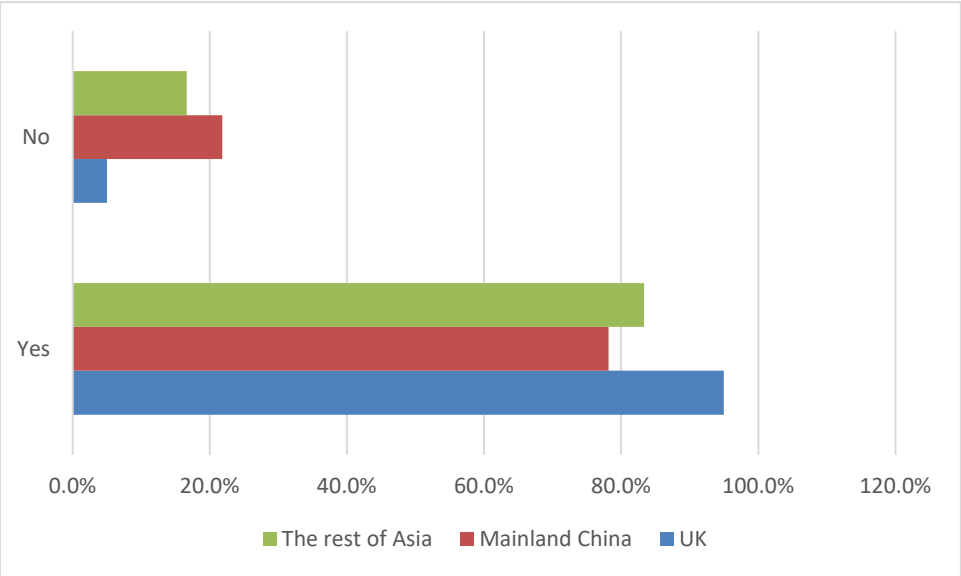


Source: IFoA Global Underwriting Survey

In the use of physical activity, the participants indicated a range of different questions. In Mainland China, 50% of those asking diabetic applicants regarding this factor asked about the duration of the activity, with 40% asking about the use of wearables and only 10% regarding the actual type of activity. In UK and the rest of Asia, there was a much more even split in use across duration use of wearables and type of activity.

The survey asked participants whether they used their diabetic applicant's smoking status in their risk assessment process. The results were very clear across all 3 regions about its use on underwriting outcomes for applicants. Smoking status was used by 95% of survey participants in the UK, lower in the rest of Asia at 84% using smoking status, but lower in Mainland China (78%), as shown in Figure 35.

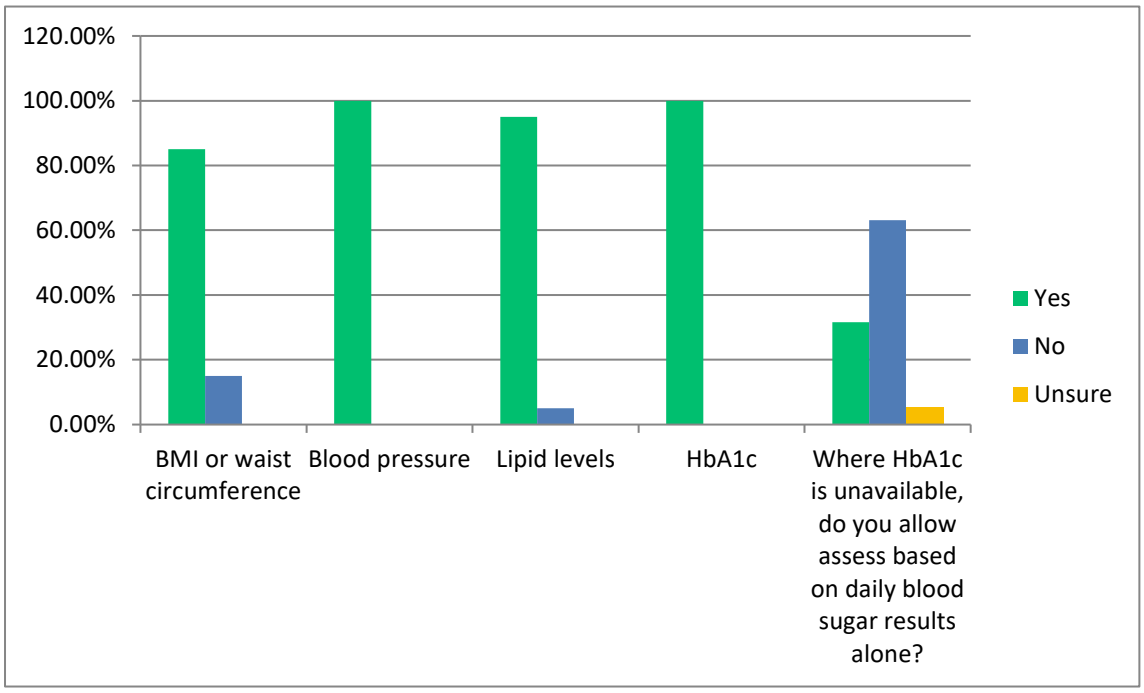
Figure 33: Use of applicant's smoking status in your risk assessment?



Source: IFoA Global Underwriting Survey

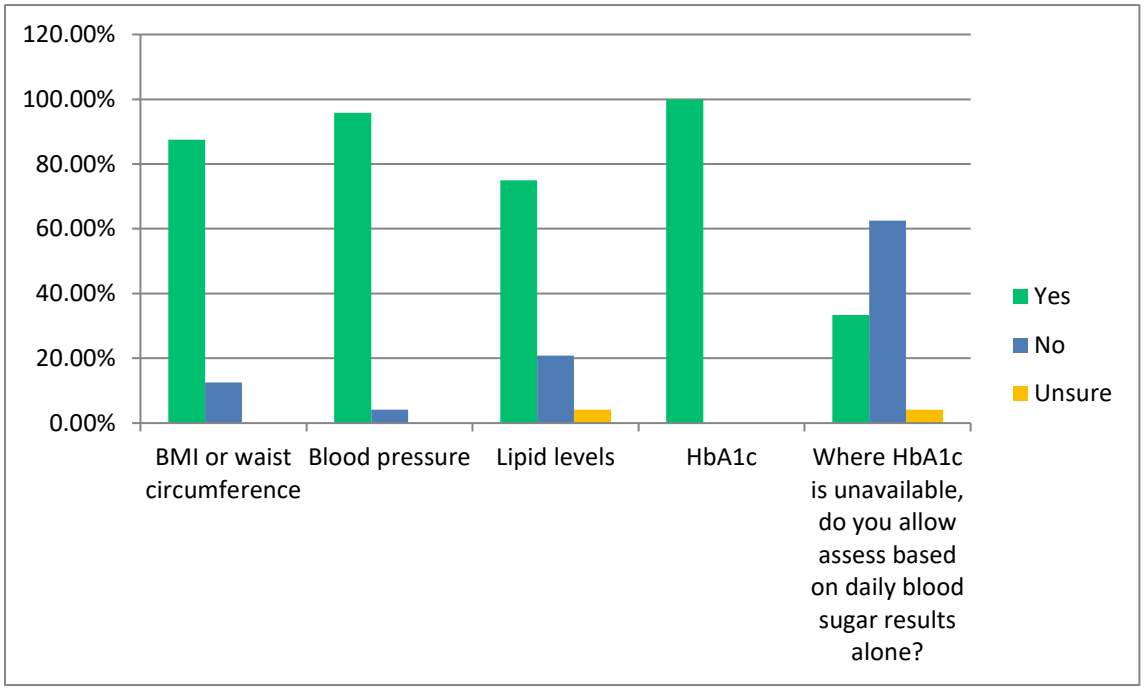
The survey asked the participants regarding about risk factors associated with increased health risk in applicants with diabetes, and the results are shown in Figure 36 (the UK) and Figure 37 (the rest of Asia and Mainland China). This shows a wide range of different factors are incorporated into underwriting assessment by insurers, providing a more individualised risk assessment and rating outcomes-based using on multiple factors. The factors focus on the overall risk profile of diabetic applicants and their cardiovascular health. There is a close association between experience in diabetics and cardiac health, and insurers are using these risk factors to assess the overall risk picture of their diabetic applicants more accurately.

Figure 34: UK: Do you use any of the following measures in your risk assessment of type 2 diabetes?



Source: IFoA Global Underwriting Survey

Figure 35: Mainland China and the rest of Asia: Do you use any of the following measures in your risk assessment of type 2 diabetes?

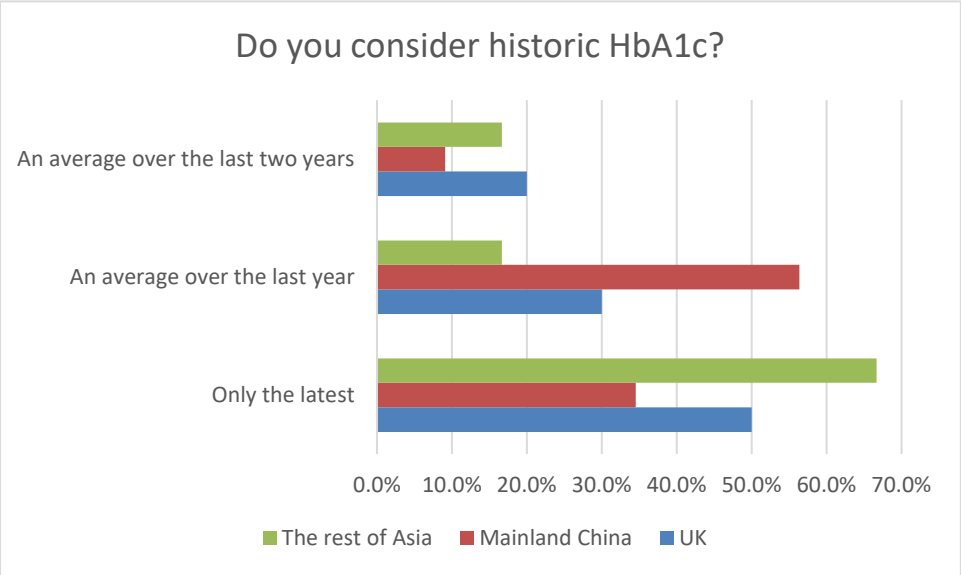


Source: IFoA Global Underwriting Survey

The use of glycated haemoglobin (HbA1c) provides a picture at a particular date of what blood sugar levels have been over a period of a few weeks or months. It is often used as an agreed criterion for the diagnosis of diabetes by national diabetic associations. Ideally, an average of recent HbA1c results should be used to assess an applicant's control and diabetic management.

The survey showed an inconsistent approach by participants in the use of HbA1c, as can be seen in Figure 38. In the rest of Asia, most insurers only use the latest HbA1c level in their risk assessment with 67%. However, this differs in the UK where 50% of participants indicate the use of the latest, while lower still in Mainland China at only 35% of participants. In Mainland China, most insurers (56%) use levels over the last year. With much fewer insurers across the 3 regions using HbA1c levels over the last 2 years. This may be explained due to less access to this data from the applicant's medical practitioner, or the applicant may only be able to state their more recent levels. However, HbA1c volatility is considered across the regions and is part of the assessment process between 75%-80% across all participants.

Figure 36: Use of historic HbA1c?



Source: IFoA Global Underwriting Survey

The participants in the UK and the rest of Asia had an almost 50-50% split on the use of vascular disease in the risk assessment of diabetic applicants with type 1 and 2 diabetes. However, the Mainland China participants showed a marked difference, with Mainland China appearing more concerned about type 1 than type 2 compared to the UK in regarding vascular disease.

Similar to physical activity, the use of diet as a risk factor for insurance has started to be more prevalent. However, the survey showed a stark contrast between such use in the risk assessment of applicants with diabetes. Diet was used in 31% of applicants, whilst only 5% of UK insurers. It highlights current differences in new risk factors used in some Asian markets, embracing new risk assessment developments.

6.5.5 Use of medical evidence in risk assessment and product outcomes

The survey asked participants about the approximate percentage of type 1 diabetes insurance applications who require the following medical evidence (Table 25).

Table 25: Medical evidence requested in the assessment of applicants with type 1 diabetes

	UK	Mainland China	The rest of Asia
GP report	27.5%	1.8%	20.0%
Medical report	17.5%	34.5%	18.2%
Diabetic clinic report	12.5%	25.5%	16.4%
Additional tests	12.5%	3.6%	21.8%
None	10.0%	27.3%	16.4%
Other	20.0%	7.3%	7.3%

Source: IFoA Global Underwriting Survey

In addition, the survey requested the approximate percentage of applications from type 2 diabetics for insurance require the following medical evidence (Table 26).

Table 26: Medical evidence requested in the assessment of type 2 diabetic applicants

	UK	Mainland China	The rest of Asia
GP report	26.8%	3.7%	20.3%
Medical report	17.1%	42.6%	20.3%
Diabetic clinic report	12.2%	27.8%	17.2%
Additional tests	12.2%	11.1%	26.6%
None	12.2%	11.1%	10.9%
Other	19.5%	3.7%	4.7%

Source: IFoA Global Underwriting Survey

Table 25 and Table 26 show the variation across the regional participants. As expected, the UK insurers make use of the national approach to the use of a single general practitioner to access the applicant's health records. This leads to Mainland China and the rest of Asia making more use of general medical examinations and additional tests to assess the risk of diabetic applicants.

6.5.6 Key messages / summary of the survey

A summary of the key observations:

- Diabetes is an important consideration in the medical underwriting process. The survey found that 91% of insurers in Mainland China have a specific question regarding diabetes; in the UK, this is 85% and much lower in the rest of Asia at 68%.
- The majority of insurers rely on reinsurers guidelines for diabetes. However, some do use their own possibly based on reinsurers. A higher proportion of UK insurers use their own guidelines (~30%) compared to Asia and Mainland China (~20%).
- The outcomes across the three regions demonstrate wide availability for life cover and mortality products, with low accessibility in relation to access to Critical Illness and disability income (Figure 24 and Figure 25)
- The number of participants asking a specific question of the applicant whether they have 'prediabetes' is considerably lower across all regions in the survey. Mainland China has a higher percentage of participants asking about pre-diabetes at 36%, with 30% in the UK and the lowest being the rest of Asia at 24%. It is an area where our research into risk factors could add further insights.
- For the key rating factors, such as age, gender and smoker status, there are differences between the different regions:
    - Age is used by 100% of insurers/reinsurers in the UK but a lower number in Mainland China and the rest of Asia. Age is a key risk factor particularly for type 2.
    - Gender is considered less in the UK compared to Mainland China and the rest of Asia, which may be to do with EU gender-neutral considerations, even though guidance indicating its use would be acceptable in relation to the different health outcomes.
    - Smoker status is an important rating factor where the UK has a higher proportion usage than Mainland China and the rest of Asia.
- Physical activity and diet are key risk factors but there is currently a low usage of physical activity and diet measurements across all regions. Mainland China has more active on using physical activity compared to UK and the rest of Asia.
- Other rating factors used such as BMI, Blood pressure, Lipid levels and HbA1c are commonly used across all regions.

7 Conclusions

People with diabetes are at increased risk of morbidity and premature death. These risks are associated with poor glycaemic control. Therefore, it's the management aim to optimise glucose parameters in those with diabetes.

Improvements in the understanding of the pathology of diabetes, as well as in management from both a medical and lifestyle perspective have led to a more positive outcome for people with diabetes; hence it is essential for insurers to understand in greater detail the risks and drivers of good and bad outcomes in those applying for insurance products who have diabetes.

This document outlines some of the key parameters that are known to be associated with mortality and morbidity risk.

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9 References

Alexander Fleming, G., Petrie, J. R., Bergenstal, R. M., Holl, R. W., Peters, A. L., & Heinemann, L. (2020). Diabetes digital app technology: Benefits, challenges, and recommendations. A consensus report by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group. *Diabetes Care*, *43*(1), 250–260. https://doi.org/10.2337/dci19-0062

Association of British Insurers. (2019). *UK Insurance and Long-Term Savings: The state of the market*. 15p. www.abi.org.uk

Bansal, N. (2015). Prediabetes diagnosis and treatment: A review. *World Journal of Diabetes*, *6*(2), 296. https://doi.org/10.4239/wjd.v6.i2.296

Campbell, P. T., Jacobs, E. J., Newton, C. C., Gapstur, S. M., & Patel, A. V. (2012). Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. *Diabetes Care*, *35*(9), 1835–1844. https://doi.org/10.2337/dc12-0002

Collier, A., Connelly, P. J., Hair, M., Cameron, L., Ghosh, S., & Waugh, N. (2018). Mortality risk remains higher in individuals with type 1 diabetes: A population-based cohort study (the Ayrshire diabetes follow-up cohort [ADOC]). *Diabetes, Obesity and Metabolism*, *20*(8), 1965–1971. https://doi.org/10.1111/dom.13334

Department of health. (n.d.). *No Title*. https://www.gov.uk/government/publications/national-service-framework-diabetes

Distiller, L. A. (2014). Why do some patients with type 1 diabetes live so long? *World Journal of Diabetes*, *5*(3), 282. https://doi.org/10.4239/wjd.v5.i3.282

Docherty, A., Harrison, E., Green, C., Hardwick, H., Pius, R., Norman, L., Holden, K., Read, J., Dondelinger, F., Carson, G., Merson, L., Lee, J., Plotkin, D., Sigfrid, L., Halpin, S., Jackson, C., Gamble, C., Horby, P., Nguyen-Van-Tam, J., … Semple, M. (2020). Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. *MedRxiv*, *April*, 1–21.

Færch, K., Witte, D. R., Tabák, A. G., Perreault, L., Herder, C., Brunner, E. J., Kivimäki, M., & Vistisen, D. (2013). Trajectories of cardiometabolic risk factors before diagnosis of three subtypes of type 2 diabetes: A post-hoc analysis of the longitudinal Whitehall II cohort study. *The Lancet Diabetes and Endocrinology*, *1*(1), 43–51. https://doi.org/10.1016/S2213-8587(13)70008-1

Ford, E. S., Zhao, G., & Li, C. (2010). Pre-Diabetes and the Risk for Cardiovascular Disease. A Systematic Review of the Evidence. *Journal of the American College of Cardiology*, *55*(13), 1310–1317. https://doi.org/10.1016/j.jacc.2009.10.060

Guo, W., Li, M., Dong, Y., Zhou, H., Zhang, Z., Tian, C., Qin, R., Wang, H., Shen, Y., Du, K., Zhao, L., Fan, H., Luo, S., & Hu, D. (2020). Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes/Metabolism Research and Reviews*, *36*(7), 1–9. https://doi.org/10.1002/dmrr.3319

Harding, J. L., Pavkov, M. E., Magliano, D. J., Shaw, J. E., & Gregg, E. W. (2019). Global trends in diabetes complications: a review of current evidence. *Diabetologia*, *62*(1), 3–16. https://doi.org/10.1007/s00125-018-4711-2

Heinemann, L., Freckmann, G., Ehrmann, D., Faber-Heinemann, G., Guerra, S., Waldenmaier, D., & Hermanns, N. (2018). Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *The Lancet*, *391*(10128), 1367–1377. https://doi.org/10.1016/S0140-6736(18)30297-6

Hirakawa, Y., Arima, H., Zoungas, S., Ninomiya, T., Cooper, M., Hamet, P., Mancia, G., Poulter, N., Harrap, S., Woodward, M., & Chalmers, J. (2014). Impact of visit-to-visit glycemic variability on

the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: The ADVANCE trial. *Diabetes Care*, *37*(8), 2359–2365. https://doi.org/10.2337/dc14-0199

Holden, S. E., Jenkins-Jones, S., Morgan, C. L., Peters, J. R., Schernthaner, G., & Currie, C. J. (2017). Prevalence, glucose control and relative survival of people with Type 2 diabetes in the UK from 1991 to 2013. *Diabetic Medicine*, *34*(6), 770–780. https://doi.org/10.1111/dme.13332

Holman, N., Forouhi, N. G., Goyder, E., & Wild, S. H. (2011). The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: Estimates of total diabetes prevalence for England, 2010-2030. *Diabetic Medicine*, *28*(5), 575–582. https://doi.org/10.1111/j.1464-5491.2010.03216.x

Huang, Y., Cai, X., Mai, W., Li, M., & Hu, Y. (2016). Association between prediabetes and risk of cardiovascular disease and all cause mortality: Systematic review and meta-analysis. *BMJ (Online)*, *355*. https://doi.org/10.1136/bmj.i5953

Huo, L., Magliano, D. J., Rancière, F., Harding, J. L., Nanayakkara, N., Shaw, J. E., & Carstensen, B. (2018). Impact of age at diagnosis and duration of type 2 diabetes on mortality in Australia 1997–2011. *Diabetologia*, *61*(5), 1055–1063. https://doi.org/10.1007/s00125-018-4544-z

Huxley, R. R., Peters, S. A. E., Mishra, G. D., & Woodward, M. (2015). Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: A systematic review and meta-analysis. *The Lancet Diabetes and Endocrinology*, *3*(3), 198–206. https://doi.org/10.1016/S2213-8587(14)70248-7

ICNARC. (2020). *ICU Audit*. https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports

Kautzky-Willer, A., Harreiter, J., & Pacini, G. (2016). Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocrine Reviews*, *37*(3), 278–316. https://doi.org/10.1210/er.2015-1137

Kosiborod, M., Gomes, M. B., Nicolucci, A., Pocock, S., Rathmann, W., Shestakova, M. V., Watada, H., Shimomura, I., Chen, H., Cid-Ruzafa, J., Fenici, P., Hammar, N., Surmont, F., Tang, F., & Khunti, K. (2018). Vascular complications in patients with type 2 diabetes: Prevalence and associated factors in 38 countries (the DISCOVER study program). *Cardiovascular Diabetology*, *17*(1), 1–13. https://doi.org/10.1186/s12933-018-0787-8

Kumar, A., Arora, A., Sharma, P., & Anil, S. (2020). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*(January), 535–545. https://www.sciencedirect.com/science/article/abs/pii/S1871402120301090?via%3Dihub

Leal, J., Gray, A. M., & Clarke, P. M. (2009). Development of life-expectancy tables for people with type 2 diabetes. *European Heart Journal*, *30*(7), 834–839. https://doi.org/10.1093/eurheartj/ehn567

Li, H., Lu, W., Wang, A., Jiang, H., & Lyu, J. (2021). Changing epidemiology of chronic kidney disease as a result of type 2 diabetes mellitus from 1990 to 2017: Estimates from Global Burden of Disease 2017. *Journal of Diabetes Investigation*, *12*(3), 346–356. https://doi.org/10.1111/jdi.13355

Livingstone, S. J., Levin, D., Looker, H. C., Lindsay, R. S., Wild, S. H., Joss, N., Leese, G., Leslie, P., McCrimmon, R. J., Metcalfe, W., McKnight, J. A., Morris, A. D., Pearson, D. W. M., Petrie, J. R., Philip, S., Sattar, N. A., Traynor, J. P., & Colhoun, H. M. (2015). Estimated life expectancy in a scottish cohort with type 1 diabetes, 2008-2010. *JAMA - Journal of the American Medical Association*, *313*(1), 37–44. https://doi.org/10.1001/jama.2014.16425

Lung, T. W. C., Hayes, A. J., Herman, W. H., Si, L., Palmer, A. J., & Clarke, P. M. (2014). A meta-analysis of the relative risk of mortality for type 1 diabetes patients compared to the general population: Exploring temporal changes in relative mortality. *PLoS ONE*, *9*(11), 1–15. https://doi.org/10.1371/journal.pone.0113635

Miller, R. G., Secrest, A. M., Sharma, R. K., Songer, T. J., & Orchard, T. J. (2012). Improvements in the life expectancy of type 1 diabetes: The pittsburgh epidemiology of diabetes complications study cohort. *Diabetes*, *61*(11), 2987–2992. https://doi.org/10.2337/db11-1625

Montvida, O., Shaw, J. E., Blonde, L., & Paul, S. K. (2018). Long-term sustainability of glycaemic achievements with second-line antidiabetic therapies in patients with type 2 diabetes: A real-world study. *Diabetes, Obesity and Metabolism*, *20*(7), 1722–1731. https://doi.org/10.1111/dom.13288

Nathan, D. M., Zinman, B., Cleary, P. A., Backlund, J. Y. C., Genuth, S., Miller, R., & Orchard, T. J. (2009). Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: The diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2. *Archives of Internal Medicine*, *169*(14), 1307–1316. https://doi.org/10.1001/archinternmed.2009.193

NDA HQIP. (2018). *National Diabetes Audit, 2016-17 Report 1: Care Processes and Treatment Targets Full Report*. *December*, 1–42. https://www.hqip.org.uk/wp-content/uploads/2018/03/National-Diabetes-Audit-2016-17-Report-1-Care-Processes-and-Treatment-T....pdf

NDA HQIP. (2019a). *National Diabetes Audit , 2017-18 Report 2b : Complications and Mortality Introduction : analysis approach*.

NDA HQIP. (2019b). National Diabetes Audit Report 2a : Complications and Mortality. *Web*, *March*.

NICE. (n.d.-a). *No Title*. https://www.nice.org.uk/guidance/conditions-and-diseases/diabetes-and-other-endocrinal--nutritional-and-metabolic-conditions/diabetes

NICE. (n.d.-b). *Type 2 diabetes: prevention in people at high risk*. 2012. https://www.nice.org.uk/guidance/ph38

Orsi, E., Solini, A., Bonora, E., Fondelli, C., Trevisan, R., Vedovato, M., Cavalot, F., Gruden, G., Morano, S., Nicolucci, A., Penno, G., & Pugliese, G. (2018). Haemoglobin A1c variability is a strong, independent predictor of all-cause mortality in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*, *20*(8), 1885–1893. https://doi.org/10.1111/dom.13306

Perreault, L., Temprosa, M., Mather, K. J., Horton, E., Kitabchi, A., Larkin, M., Montez, M. G., Thayer, D., Orchard, T. J., Hamman, R. F., & Goldberg, R. B. (2014). Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: Results from the diabetes prevention program outcomes study. *Diabetes Care*, *37*(9), 2622–2631. https://doi.org/10.2337/dc14-0656

Rawshani, Aidin, Rawshani, A., Franzén, S., Eliasson, B., Svensson, A.-M., Miftaraj, M., McGuire, D. K., Sattar, N., Rosengren, A., & Gudbjörnsdottir, S. (2017). Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *New England Journal of Medicine*, *376*(15), 1407–1418. https://doi.org/10.1056/nejmoa1608664

Rawshani, Araz, Sattar, N., Franzén, S., Rawshani, A., Hattersley, A. T., Svensson, A. M., Eliasson, B., & Gudbjörnsdottir, S. (2018). Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *The Lancet*, *392*(10146), 477–486. https://doi.org/10.1016/S0140-6736(18)31506-X

Rodríguez-Poncelas, A., Mundet-Tudurí, X., Miravet-Jiménez, S., Casellas, A., Barrot-De La Puente, J. F., Franch-Nadal, J., & Tuero, G. C. De. (2016). Chronic Kidney Disease and Diabetic Retinopathy in Patients with Type 2 Diabetes. *PLoS ONE*, *11*(2), 1–10. https://doi.org/10.1371/journal.pone.0149448

Shah, A. D., Langenberg, C., Rapsomaniki, E., Denaxas, S., Pujades-Rodriguez, M., Gale, C. P., Deanfield, J., Smeeth, L., Timmis, A., & Hemingway, H. (2015). Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1·9 million people. *The Lancet Diabetes and Endocrinology*, *3*(2), 105–113. https://doi.org/10.1016/S2213-8587(14)70219-0

Sherwood Z. (2018). *Journal of Diabetes Nursing*, *22*(3). https://diabetesonthenet.com/wp-content/uploads/pdf/dotn29cddf1e36a84b3c1511d3f10d55b372.pdf

Smith, J. J., Wright, D. M., Scanlon, P., & Lois, N. (2020). Risk factors associated with progression to referable retinopathy: a type 2 diabetes mellitus cohort study in the Republic of Ireland. *Diabetic Medicine*, *37*(6), 1000–1007. https://doi.org/10.1111/dme.14278

Soedamah-muthu, S. S., Vergouwe, Y., Costacou, T., Miller, R. G., Zgibor, J., Chaturvedi, N., Snell-bergeon, J. K., Maahs, D. M., Forsblom, C., Harjutsalo, V., Groop, P., & Fuller, J. H. (2015). *development and validation study*. *57*(11), 2304–2314. https://doi.org/10.1007/s00125-014-3358-x.Predicting

Tabák, A. G., Herder, C., Rathmann, W., Brunner, E. J., & Kivimäki, M. (2012a). Prediabetes: A high-risk state for diabetes development. *The Lancet*, *379*(9833), 2279–2290. https://doi.org/10.1016/S0140-6736(12)60283-9

Tabák, A. G., Herder, C., Rathmann, W., Brunner, E. J., & Kivimäki, M. (2012b). Prediabetes: A high-risk state for diabetes development. *The Lancet*, *379*(9833), 2279–2290. https://doi.org/10.1016/S0140-6736(12)60283-9

Tabák, A. G., Jokela, M., Akbaraly, T. N., Brunner, E. J., Kivimäki, M., & Witte, D. R. (2009). Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *The Lancet*, *373*(9682), 2215–2221. https://doi.org/10.1016/S0140-6736(09)60619-X

Tancredi, M., Rosengren, A., Svensson, A.-M., Kosiborod, M., Pivodic, A., Gudbjörnsdottir, S., Wedel, H., Clements, M., Dahlqvist, S., & Lind, M. (2015). Excess Mortality among Persons with Type 2 Diabetes. *New England Journal of Medicine*, *373*(18), 1720–1732. https://doi.org/10.1056/nejmoa1504347

Tauschmann, M., Thabit, H., Bally, L., Allen, J. M., Hartnell, S., Wilinska, M. E., Ruan, Y., Sibayan, J., Kollman, C., Cheng, P., Beck, R. W., Acerini, C. L., Evans, M. L., Dunger, D. B., Elleri, D., Campbell, F., Bergenstal, R. M., Criego, A., Shah, V. N., … Yong, J. (2018). Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *The Lancet*, *392*(10155), 1321–1329. https://doi.org/10.1016/S0140-6736(18)31947-0

Timar, B., & Albai, O. (2013). The relationship between hemoglobin a1c and chronic complications in diabetes mellitus. *Romanian Journal of Diabetes Nutrition and Metabolic Diseases*, *19*(2), 115–122. https://doi.org/10.2478/v10255-012-0015-3

Vistisen, D., Witte, D. R., Tabák, A. G., Herder, C., Brunner, E. J., Kivimäki, M., & Færch, K. (2014). Patterns of Obesity Development before the Diagnosis of Type 2 Diabetes: The Whitehall II Cohort Study. *PLoS Medicine*, *11*(2). https://doi.org/10.1371/journal.pmed.1001602

Webber, S. (2013). International Diabetes Federation. In *Diabetes Research and Clinical Practice* (Vol. 102, Issue 2). https://doi.org/10.1016/j.diabres.2013.10.013

White, M., Sabin, M. A., Magnussen, C. G., O'Connell, M. A., Colman, P. G., & Cameron, F. (2017). Long term risk of severe retinopathy in childhood-onset type 1 diabetes: A data linkage study. *Medical Journal of Australia*, *206*(9), 398–401. https://doi.org/10.5694/mja16.00712

WHO. (2016). Global Report on Diabetes. *Isbn*, *978*, 6–86. https://apps.who.int/iris/handle/10665/204871

WHO. (2020). *Top 10 causes of death*. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

WHO. (2021). *Diabetes Fact Sheet*. https://www.who.int/news-room/fact-sheets/detail/diabetes

Williamson, E. J., Walker, A. J., Bhaskaran, K., Bacon, S., Morton, C. E., Curtis, H. J., Mehrkar, A., Evans, D., Cockburn, J., Mcdonald, H. I., Mackenna, B., Tomlinson, L., Douglas, I. J., Rentsch, C. T., Mathur, R., Wong, A. Y. S., Grieve, R., Harrison, D., Forbes, H., … Smeeth, L. (2021). Europe PMC Funders Group OpenSAFELY : factors associated with COVID-19 death in 17

million patients. *Nature*, *584*(7821), 430–436. https://doi.org/10.1038/s41586-020-2521-4.OpenSAFELY

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