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James Lind Alliance Research Priorities

How do we identify people at high risk of Type 2 diabetes and help prevent the condition from developing?

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Aims To review the evidence regarding the identification of those at high risk of Type 2 diabetes and the conceptual and clinical criteria defining high risk, the prevention or delay of onset of Type 2 diabetes through lifestyle interventions, and the evolution of evidence from efficacy trials, through effectiveness trials in real-world settings, to implementation programmes at scale.

Method The wide scope of this review precluded a systematic approach, therefore, we present a narrative review that highlights key themes and contemporary developments, drawing on landmark studies, previous systematic and expert reviews, and previous meta-analyses.

Results While the diagnostic thresholds for Type 2 diabetes are accepted, international consensus on whether, and how, to classify those at high risk of Type 2 diabetes has not been achieved. There is ongoing debate about which laboratory test to use and each test's corresponding inclusion threshold, about where the balance of clinical benefits and harms sit when defining thresholds, and about how affordability of subsequent preventative interventions might influence the derivation of such thresholds within any particular population. A remarkable international effort has seen the evolution of interventions for those at high risk move from efficacy trials, through effectiveness trials, to implementation at scale, and the evidence supporting each stage is reviewed.

Conclusions To achieve healthcare system sustainability, many countries are now focusing on disease prevention. To complement population-level interventions that address the obesogenic environment, lifestyle interventions that empower individuals at high risk of Type 2 diabetes to modify this risk beneficially are now being implemented at scale.

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Introduction

The health, social and economic burdens of Type 2 diabetes at a global and national level are well established [1]. Excess morbidity and premature mortality are burdens borne by individuals, their families and their carers, with additional social impacts on, for example, employment. Data from the International Diabetes Federation (IDF) suggest that globally, 425 million adults (8.8%) aged 18–79 years were living with diabetes in 2017 [2]. Age-standardized prevalence nearly doubled, from 4.7% in 1980 to 8.5% in 2014 [1]. Approximately 90% of people with diabetes have Type 2 diabetes, and globally 30–80% of those with Type 2 diabetes are estimated to be undiagnosed. Data, again from the IDF, suggest that in the UK, 2.7 million adults [5.9% (95% CI 5.2–7.9)] had diabetes in 2017, with 508 000 as yet undiagnosed [2]. The direct health costs for diabetes in the UK were estimated to be £9.8 bn in the financial year 2010/2011, ~10% of the total health resource expenditure [3].

The global increase in prevalence of Type 2 diabetes has tracked the increase in prevalence of overweight and obesity as the major modifiable risk factor. Worldwide, the WHO estimates that obesity has nearly tripled since 1975, and in 2016, more than 1.9 billion (39%) adults (≥18 years) were overweight, and 650 million (13%) were obese [4]. High-income countries are particularly affected, with 30% of the adult population (≥18 years) estimated to be obese in the UK [4]. Preventing and treating overweight and obesity is required in order to affect Type 2 diabetes incidence, and multi-sectoral population approaches such as the UK Government's Childhood Obesity Plan [5,6] must therefore be central elements of national strategies to prevent Type 2 diabetes.

The James Lind Alliance Research Prioritization has ranked highly the themes of identifying people at high risk of Type 2 diabetes, and preventing the condition from developing in the

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What's new?

- Efficacy and effectiveness trials have shown that lifestyle interventions can prevent or delay the onset of Type 2 diabetes in those at high risk. To complement population-level interventions that address the obesogenic environment, there is now an international focus on lifestyle interventions that empower individuals at high risk of Type 2 diabetes to modify that risk beneficially and on the implementation of such interventions at scale.
- While the diagnostic thresholds for Type 2 diabetes are accepted, international consensus on whether, and how, to classify those at high risk of Type 2 diabetes has not been achieved. There is ongoing debate about which laboratory test to use, each test's corresponding inclusion threshold, where the balance of clinical benefits and harms sit when defining thresholds, and how affordability of subsequent preventative interventions might influence the derivation of such thresholds within any particular population. The present review explores these themes and summarizes an international effort that has seen the evolution of interventions for those at high risk move from efficacy trials, through effectiveness trials, to implementation at scale.
- The review outlines the processes of clinical identification of those at high risk of Type 2 diabetes and how defining high risk may be refined in future. In countries where programmes are being implemented at scale, identification of those at high risk can now lead to access to lifestyle interventions that have the potential to modify that risk beneficially.

people thus identified. The scope of the present review is, therefore, the identification of those at high risk of Type 2 diabetes and the conceptual and clinical criteria defining high risk, the prevention or delay of onset of Type 2 diabetes through lifestyle interventions and the evolution of evidence from efficacy trials, through effectiveness trials in real-world settings, to implementation of programmes at scale, and, following adoption in policy and implementation, the challenges observed and how they might be addressed in the future.

The wide scope precluded a systematic review approach, therefore, the article is a narrative review that highlights key themes and contemporary developments, drawing on landmark studies, previous systematic and expert reviews and previous meta-analyses.

Identification

While the diagnostic thresholds for Type 2 diabetes are accepted, international consensus on whether and how to classify those at high risk of Type 2 diabetes has not been achieved. Identifying those at high risk of developing Type 2 diabetes requires a detailed understanding of the relationships between epidemiological and clinical risk factors, in addition to laboratory test results. At a global level these relationships are likely to vary within and between countries and populations in ways which are not yet fully understood [1]. There is ongoing debate about which test to use and each test's corresponding inclusion threshold, where the balance of clinical benefits and harms sit when defining such a threshold, and how affordability of subsequent appropriate preventative interventions might influence the derivation of such thresholds in different populations.

Formal classifications have tended to rely on laboratory test results. One or more of three tests are used to define the diagnostic thresholds for Type 2 diabetes diagnosis, and a second lower inclusion threshold to define high risk. The three tests are: the 2-h 75-g oral glucose tolerance test (OGTT) glucose value, fasting plasma glucose (FPG) value, and HbA_{1c} value. Test values between the high risk inclusion and diagnostic thresholds for any one of the tests may be used to classify individuals as high risk, and eligible for targeted interventions to prevent Type 2 diabetes. Table 1 outlines the different descriptors of high risk using each test or combination of tests, and their definitions.

Epidemiology of those classified as at high risk

The capacity of the healthcare system and wider society to identify and prevent Type 2 diabetes amongst those at high risk varies markedly at a global level [1], as does the capacity to treat Type 2 diabetes once diagnosed. While there are well developed systems for population surveillance, diagnosis and treatment in high-income countries, many countries lack epidemiological information quantifying the associations between risk factors and Type 2 diabetes.

Table 1 Descriptors of high risk of Type 2 diabetes and their laboratory test-based definitions

Descriptor	Definition
WHO-defined IFG	FPG 6.1–6.9 mmol/l
ADA-defined IFG	FPG 5.6–6.9 mmol/l
IGT	FPG <7.0 mmol/l and 2-h post-75-g OGTT glucose value ≥7.8 mmol/l and <11.1 mmol/l
Impaired glucose regulation	IFG as defined by WHO and/or IGT
Prediabetes (defined by the ADA)	FPG 5.6–6.9 mmol/l and/or HbA_{1c} 39–47 mmol/mol (5.7–6.4%) and/or 2-h post-75-g OGTT glucose value ≥7.8 mmol/l and <11.1 mmol/l
Non-diabetic hyperglycaemia	FPG 5.5–6.9 mmol/l and/or HbA_{1c} 42–47 mmol/mol (6.0–6.4%)

ADA, American Diabetes Association; FPG, fasting plasma glucose; IFG, Impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

A recent prevalence study in India, for example, estimated variation in risk factor and diabetes prevalence (Type 1 and Type 2 not distinguished) across the country [7]. Sample surveys of 15 Indian states highlighted marked variations between and within states. The authors noted socio-economic patterning of prevalence, which was indicative of epidemiological transition for diabetes within India [7]. Specifically, the authors cited previous reports showing that diabetes was more prevalent amongst those with the highest socio-economic status. In contrast, the more recent data suggested that this pattern was actually confined to rural areas, whilst in urban areas prevalence was now higher in lower socio-economic groups. This shift in prevalence to those with lower socio-economic status is similar to that observed in high-income countries and increases the urgency for comprehensive preventative intervention as lower socio-economic groups typically have less access to healthcare for Type 2 diabetes treatment internationally [7].

In contrast to low- and middle-income countries, in high-income countries prevalence and variation in that prevalence is now increasingly well understood, both for Type 2 diabetes and for various definitions of high risk. In England, the prevalence of non-diabetic hyperglycaemia was 10.7% (95% CI 10.2–11.1) of the adult population, equating to ~ 5 million adults [8]. In this case, non-diabetic hyperglycaemia prevalence estimates were based on HbA1c values of 42–47 mol/mol (6.0–6.4%) measured in nationally representative Health Survey for England data, pooled from 2009–2013.

Identification in clinical practice

In clinical practice, epidemiological, clinical and laboratory risk factor information is often assimilated into a two-step process. In England, National Institute of Health and Care Excellence (NICE) Public Health Guideline 38 (PH38) recommends that clinicians use a validated risk tool for the first step [9]. These include the Leicester Practice Risk Score (LPRS), the Cambridge Diabetes Risk Score (CDRS), the Leicester Risk Assessment Tool (LRAT), the Finland Diabetes Risk Score (FINDRISC), and the Q-Diabetes tool. Most tools use cross-sectional epidemiological associations between Type 2 diabetes risk factors and Type 2 diabetes prevalence (LPRS, CDRS, LRAT and FINDRISC), while Q-Diabetes uses longitudinal data to derive 10-year risk of Type 2 diabetes incidence, to identify those at high risk.

The risk scores cited by NICE are based on a wide range of demographic and clinical risk factors for Type 2 diabetes. All risk factors used by any NICE-recommended risk scores are listed for completeness, and include: age; sex; ethnicity (groups vary by national context); physical activity; fruit and vegetable consumption; socio-economic status; BMI; waist circumference; smoking history; family history of diabetes in a first degree relative; diagnosis of cardiovascular disease; diagnosis of hypertension or prescribed antihypertensive medication; prescribed corticosteroid medication; diagnoses of schizophrenia or bipolar affective disorder, learning disability, gestational diabetes or polycystic ovarian syndrome; prescribed second-generation atypical antipsychotic medication; and prescribed statin medication. Q-Diabetes 2018 has the most comprehensive risk factor inclusion, involving predictors such as diagnosis of gestational diabetes, learning disability and schizophrenia, predictors which are of relatively low prevalence in the population, but for which the relative risks of developing Type 2 diabetes are particularly high [10].

For the second step, those identified as high risk using risk tools are offered a blood test. While, in principle, any of the three tests (OGTT, FPG and HbA_{1c}) could be used, in England, NICE recommends FPG or HbA_{1c} [9]. The blood test results then determine formal categorization in England, as normoglycaemia (at low to moderate risk), non-diabetic hyperglycaemia (high risk; Table 1), or newly diagnosed Type 2 diabetes (although in the absence of osmotic symptoms, diagnosis of Type 2 diabetes requires a second confirmatory blood test by the same method (FPG or HbA_{1c}). Risk classifications then determine subsequent clinical pathways, as described in guidelines [9].

Risk tools to date tend, therefore, to support identification, but do not determine final classification; however, recent work on the 2018 update for Q-Diabetes [10] suggests that a second step which draws together all risk factors—epidemiological and clinical factors, and laboratory results (FPG or HbA_{1c})—may increase performance of the identification process to identify those at high risk. Comparison of algorithms that combine blood tests and risk tools vs blood tests in isolation showed that the combined algorithms performed better, especially those that included HbA1c values [10]. Further validation is required, along with improving underlying data quality (only 16% of the cohort had complete HbA_{1c}, BMI and smoking records), but results support a potential way to improve the identification of those at high risk.

Inclusion thresholds for those at high risk of Type 2 diabetes

The diagnostic thresholds for Type 2 diabetes [11.1 mmol/l, 7.0 mmol/l and 48 mmol/mol (6.5%) for OGTT, FPG and HbA_{1c}, respectively] are accepted internationally as the values above which one can see development of the diabetic microvascular complications of retinopathy. It is recognized that the prevalence of Type 2 diabetes in populations will not be exactly the same when using each of these three different tests for diagnosis, and that near the diagnostic thresholds each test will not necessarily identify exactly the same individuals [11].

Conceptually, 'high risk' describes those who are at a higher risk of progressing to Type 2 diabetes within a defined time period than those who are classified as 'low to moderate risk'; however, 'operationalizing' the concept through blood tests is not straightforward, as Type 2 diabetes risk is a continuum. While there is a consistent international threshold

for high risk using the 2-h post-OGTT glucose value (≥7.8 mmol/l), the OGTT is expensive and impractical to perform in routine clinical environments. Nevertheless, the landmark Type 2 diabetes prevention trials (described below) used the 2-h post-OGTT glucose value for inclusion. In contrast, although HbA_{1c} and FPG tests are easy to perform in routine clinical environments, the fact that they have not been used explicitly as inclusion criteria in the landmark Type 2 diabetes prevention trials has led some to question their validity in defining high risk [12]. Related to this, the recommended values for FPG and HbA_{1c} vary by organization and country, as outlined in Table 1, and at the last assessment, the WHO considered that there was insufficient evidence to define a high risk threshold using HbA_{1c} [13].

Greater rate of progression to Type 2 diabetes in those at high risk

Despite the lack of consensus, all definitions of high risk are associated with greater rates of progressing to Type 2 diabetes, as reported in a meta-analysis of progression rates across 70 studies in participants for whom different definitions of high risk were used at baseline [14]. Pooled incidence rates were calculated using Bayesian random-effects models and showed that rates were not statistically different when calculated for different definitions of high risk at baseline. Specifically, studies using elevated HbA_{1c} [42–47 mmol/mol (6.0–6.4%)] found a pooled incidence rate of 35.6 per 1000 person-years [six studies (95% CI 15.1–83.0)]. This was a similar magnitude but had wider credible intervals (probably attributable to smaller sample size) than those calculated for American Diabetes Association (ADA)-defined impaired fasting glucose [IFG; 11 studies, 35.5 (95% CI 26.6–48.0)]. Both were non-significantly lower than WHO-defined IFG [34 studies, 47.4 (95% CI 37.4–59.8)] and impaired glucose tolerance [IGT; 46 studies, 45.5 (95% CI 37.8–54.5)]. The combination of IFG (the authors did not report whether this was ADA- or WHO-defined IFG) and IGT [15 studies, 70.4 (95% CI 53.8–89.7)] was of a higher magnitude in terms of predictive power, reflecting the increased specificity of requiring identification by two co-existent high-risk definitions, but the credible interval still overlapped with all definitions except ADA-defined IFG which was significantly lower. The use of glucose-based tests compared with HbA_{1c} values also identified different Type 2 diabetes groups at follow-up, which also contributed to variations in progression rates. The authors did not report searching for, or finding, studies using HbA_{1c} [39–47 mmol/mol (5.7–6.4%)] at baseline or follow-up.

Greater risk of cardiovascular disease in those at high risk of Type 2 diabetes

People at high risk of Type 2 diabetes are at increased risk of cardiovascular disease. In the European Prospective Investigation of Cancer (EPIC)-Norfolk study, a 1% increase in HbA_{1c} within the normal range (under the diagnostic threshold for Type 2 diabetes) was associated with increased 10-year cardiovascular mortality [15]. This finding is supported by a meta-analysis of 53 prospective observational studies. Those classified as high risk using the ADA or WHO definitions of IFG (Table 1) were at higher risk of incident cardiovascular disease, stroke and all-cause mortality, while those defined as high risk using HbA_{1c} definitions [39–47 mmol/mol (5.7–6.4%) or 42–47 mmol/mol (6.0–6.4%)] were at greater risk of composite cardiovascular disease and coronary heart disease [16]. HbA_{1c} is a measure of protein glycation, and interestingly, in another study, HbA_{1c}-based definitions of high risk performed slightly better than glucose-based definitions in predicting cardiovascular disease and all-cause mortality [17].

People who are at high risk are therefore more likely to develop Type 2 diabetes and cardiovascular disease, although there will always be significant numbers of this large population group who will never go on to develop either. This underscores the need to continually refine the performance of risk tools with the latest epidemiological knowledge and clinical data [10].

Is there risk of microvascular disease in those at high risk of Type 2 diabetes?

Although not formally characterized histologically as relating to hyperglycaemia, prediabetes is associated with a higher prevalence of chronic kidney disease [18]. There is also a higher prevalence of peripheral neuropathy in prediabetes, but the relationship to hyperglycaemia is unclear [19]. It is not known if interventions, whether lifestyle or pharmacotherapeutic, to address prediabetes will affect such associations. While the original Da Qing Chinese efficacy interventional trial (further details below) showed a reduction in risk of diabetic retinopathy at 20 years [20], it has been assumed that this was mediated via reduced Type 2 diabetes incidence in the intervening time, rather than via a direct association between IGT and diabetic microvascular disease.

Affordability and identification inclusion criteria

Affordability is an important consideration when setting identification thresholds for high risk. The lower the inclusion threshold, the larger the population of those defined as high risk, and the larger the resources required to deliver intervention programmes to those at risk. Additionally, lower inclusion thresholds are associated with higher test sensitivity and lower specificity, meaning that the cohort is diluted with a higher proportion of those never destined to develop Type 2 diabetes. This leads to smaller average risk reduction with interventions (lower effectiveness) and lower cost-effectiveness [21]. Work has been undertaken using

scenario modelling to understand the interplay of these factors when combined with variations in test performance of different combinations of formal risk assessment tools and blood tests [22]. This work has shown that higher test performance was achieved at a higher economic cost and lower practicality. These type of data are important to inform the optimization of case-finding and prevention protocols for prevention of those at high risk of Type 2 diabetes.

For many of the reasons outlined above, there is an ongoing uncertainty around the value of population screening for Type 2 diabetes. In the UK, the case for population screening is considered on an ongoing basis through scheduled evidence reviews by the UK National Screening Committee [23]. Of particular interest in the debate is the fact that those at high risk of Type 2 diabetes, and those currently living with undiagnosed Type 2 diabetes, would both be identified in screening tests (e.g. the glucose-based tests and HbA_{1c} discussed above). An important change in context since the previous review is that, in England, there is now a comprehensive service, which could potentially accept referrals from a population screening programme identifying those at high risk (described below).

Prevention

Efficacy trials of lifestyle interventions

Landmark randomized controlled trials (RCTs) show that progression to Type 2 diabetes amongst those at high risk (defined as those with IGT in the trials) can be prevented or delayed through intensive lifestyle behavioural change interventions to promote weight loss, better quality nutrition, and increased physical activity [24–28]. Results from the Finnish Diabetes Prevention Study (FDPS) and US Diabetes Prevention Programme demonstrated reductions in the cumulative incidence of Type 2 diabetes: by 58% (95% CI 48–66) over a 2.8-year period in the US DPP [25] and by 58% (95% CI 30–70) over 3.2 years in the FDPS [24]. Type 2 diabetes risk in the US DPP was found to decrease with moderate weight loss; every 1-kg decrease in weight in the lifestyle arm was associated with a 16% reduction in future Type 2 diabetes incidence [29]. A recent Cochrane systematic review and meta-analysis [30] of 11 RCTs including 4511 participants demonstrated a 43% reduction in risk (95% CI 36–50) over a mean follow-up of 3.8 years.

Three of the landmark RCTs [24–26] have described longer-term outcomes. The 13-year post-baseline follow-up of the FDPS demonstrated significant between-group reductions in Type 2 diabetes incidence of 39% (95% CI 21–52) [31]. Compared with placebo, diabetes incidence at mean 15-year follow-up was reduced in the US DPP by 27% (95% CI 17–35) [32]. The 23-year follow-up of the Da Qing trial (n=542, 94% of original cohort) reported significant differences in the cumulative incidence of Type 2 diabetes of 76.6% (95% CI 68.4–76.8) in the intervention arm and 89.9% (95% CI 84.9–94.9) in the control group, with all-cause mortality [intervention 28.1% (95% CI 23.9–32.4) vs control 38.4% (95% CI 30.3–46.5)] also significantly lower [33]. A 20-year follow-up study of the Da Qing trial also found reductions in incidence of severe diabetic retinopathy [20].

Efficacy trials of pharmacotherapeutic interventions

While not the specific focus of the present review, a number of RCTs have demonstrated the efficacy of certain drugs, glucose-lowering and weight loss-promoting, to prevent or delay onset of Type 2 diabetes in those at high risk [34]. Studies have included metformin [25,28], α-glucosidase inhibitors [35,36], thiazolidinediones [37–41], a glucagon-like peptide-1 (GLP-1) agonist [42], glargine insulin [43] and the lipase inhibitor orlistat [44]. A recent retrospective longitudinal study assessed the potential beneficial role for combination therapy with metformin, a thiazolidinedione and a GLP-1 agonist, which the authors suggest addresses the underlying physiological deficits [45]. Effect sizes in some of the drug studies have been similar in magnitude to those seen in other studies for lifestyle interventions [34]. There were interesting differences in efficacy of thiazolidinediones according to ethnicity [37,38]. The potential for drug side effects must be weighted more heavily when considering cohorts at high risk, in which proportions are never destined to develop Type 2 diabetes, than when treating hyperglycaemia in cohorts that already have Type 2 diabetes. Furthermore, concerns about the over-medicalization of healthy populations through drug prescribing have been expressed, and when compared to lifestyle interventions, a meta-analysis of RCTs assessing weight loss- and insulin-sensitizing medications demonstrated no sustained effect post-drug intervention [46].

Translation to real-world settings: from efficacy trials to evaluative studies

The lifestyle interventions included in efficacy trials were intensive, with one-to-one sessions and long periods of delivery and maintenance (the Da Qing intervention lasted 6 years), and prohibitively expensive to deliver at scale [47]. Translation into real-world settings is therefore a major challenge; the aim is to design interventions with clinically meaningful effectiveness whilst also being deliverable and affordable in the real world [34,48].

Multiple evaluative studies have been conducted [34], including the Good Ageing in Lahti Region (GOAL) translation of the FDPS [49,50] and the MOVE! Weight Programme for Veterans translation of the US DPP [51].

A systematic review and meta-analysis of 36 studies examined weight change and Type 2 diabetes incidence in pragmatic and controlled prevention studies over a 12–18-

month follow-up period [52]. Reported summary effects included reduction in Type 2 diabetes incidence of 26% (incidence rate ratio 0.74, 95% CI 0.58–0.93) across 13 real-world RCTs. Across the 20 RCTs measuring weight, between-group weight change was –1.57 kg (95% CI –2.28 to –0.86). Within-group weight change across 35 controlled and uncontrolled studies over the same follow-up was –2.46 kg (95% CI –2.99 to –1.94). A US-based systematic review and meta-analysis [53] of 28 controlled and uncontrolled studies found a clinically meaningful summary effect on mean percentage weight change at 12 months of –3.99% (95% CI –5.16 to –2.83).

Subgroup and meta-regression analyses in systematic reviews of Type 2 diabetes prevention programmes [48,52,53] highlight factors for increased effectiveness following translation. These include larger numbers of sessions, 9–18-month programme duration, social support, and adherence to guidelines [e.g. NICE and Implementation of a European Guideline and Training Standards for Diabetes Prevention (EU-IMAGE) guidelines]. Effectiveness was not compromised by lay community member delivery as opposed to healthcare professional delivery [53].

Effect sizes observed in efficacy trials are attenuated somewhat following translation [34,48,54]. For example, the risk reduction for Type 2 diabetes associated with the US DPP trial was 58% (95% CI 48–66), and was 33% (95% CI 26–39) for 'intensely engaged' participants of the MOVE! Programme [51]. Attenuation is attributable to many factors. Trial participants are likely to be more motivated than those in real-world services [54], and the intensity of real-world programmes is typically lower following translation [52]; however, despite attenuation, observed reductions in weight are positive as people who are at high risk are typically expected to experience a weight increase on average [55]. Furthermore, even 1-kg weight loss is associated with a 16% reduction in Type 2 diabetes risk, as noted above [29].

Overall, research suggests that it is feasible to translate lifestyle interventions included in Type 2 diabetes efficacy trials to real-world settings, and that the translations can deliver clinically meaningful changes in outcomes.

Delivery of individual-level lifestyle interventions at scale

Understanding how to scale up Type 2 diabetes prevention to large populations and incorporate prevention for those at high risk into routine practice is growing [21,34]. To inform this process, knowledge is required about a wide range of factors which move from sole considerations of clinical effectiveness to also encompass implementation factors (reach, effectiveness, adoption, uptake, retention, maintenance), population health factors (population effectiveness, effect on inequalities), commissioning factors (cost-effectiveness, affordability, healthcare capacity, workforce, fidelity, quality assurance) and political factors (long-term strategic commitment to prevention) [21].

Implementation at scale was taken forward through the Finland National Programme for the Prevention of Type 2 Diabetes (FIN-D2D), which covers five hospital districts and 1.5 million people [55]. This was followed by state-wide efforts through the Life! study in Australia [21] and the launch of a national Type 2 diabetes prevention framework in the USA [56]. A recent development has been the NHS DPP in England, which achieved 100% geographical coverage in England in 2018 [57]. Other countries such as Singapore and Israel are also launching prevention programmes, illustrating the increasing international interest in these approaches [34].

Programmes delivered at scale are associated with clinically meaningful changes in outcomes or surrogate outcomes. FIN-D2D follow-up data (n=2798, pre-post uncontrolled study), reported reduced Type 2 diabetes incidence by 69% (relative risk 0..31, 95% CI 0.16–0.59) in the 17.5% of the participants who lost >5% of their body weight [55]. Average weight loss across all participants was 1.2 kg. The Melbourne Diabetes Prevention Study [58] tested the effectiveness of Life! using a parallel-group RCT design (n=342). Using per-protocol-set analysis, participant weight change was –1.13 kg (P=0.016), while intention-to-treat analysis suggested a smaller and non-significant change of –0.89 kg (P=0.079). No significant changes in glycaemic control (FPG values from OGTT) were observed in either per-protocol-set or intention-to-treat findings, although cardiovascular disease risk factors were improved. The authors present per-protocol findings as the primary analysis, arguing that health service planning needs to be based on those who take part in interventions. In the US DPP (again uncontrolled) pre-post evaluation study, 14 747 adults were enrolled in the programme, and 35.5% of the 13 893 with valid weight data lost > 5% of their baseline weight, with an average of 4.2% weight loss [59]. Outcomes data from the NHS DPP are not yet available but are anticipated [57].

In at-scale programmes, increasing retention is important [59]. In the US DPP, 43% of participants completed 16/23 offered sessions. Participant retention increases sessions attended, and therefore effectiveness; in the US DPP study each additional session attended was associated with an additional 0.31 kg of weight loss [59]. A behavioural analysis of uptake and retention in group-based weight management suggests that social support, programme flexibility, educational requirements of programmes, and offering a range of behaviour change techniques may be important [60]. One of the lessons learnt from the Life! study scale-up process was that payment models should be used to incentivize retention [21].

Programmes can also draw on evidence to specify core programme elements such as curricula, workforce, intensity, length, and mode of delivery, as noted in the course of the US DPP, NHS DPP and Life! scale-up approaches [21,59]. It is also critical that programmes are theoretically informed, and that commissioners and providers are clear about the theory of change that should underpin the programme. This is

particularly the case where programmes are being translated from one international setting to another [61].

Increasing the reach of lifestyle programmes to increase population impact is a major challenge, and as already discussed, requires both targeted and population-wide approaches [12,62]. In targeted lifestyle programmes, scalability can be increased by shifting from face-to-face delivery to less resource-intensive 'remote' modes such as digital and telehealth [63]. This is likely to be particularly important for delivery in low- and middle-income countries, and to increase access for groups where face-to-face provision is less acceptable [63]. Whether remote delivery increases cost-effectiveness depends on whether delivery through these modes attenuates effectiveness relative to face-to-face delivery. There is growing evidence that remote approaches are effective relative to usual care. An India-based RCT (n=537) of a text-messaging intervention demonstrated a 36% reduction in cumulative Type 2 diabetes incidence over 24 months (95% CI 8–55) in the intervention compared with the control group [64]. More recently, a US-based RCT (n=339) showed statistically significant between-group improvement in glycaemic control (FPG), weight and cardiovascular disease risk at 6-month follow-up [65]. Meta-analysis [66] of 18 controlled and uncontrolled longitudinal studies (n=2774 participants) over a 12-week to 2-year follow-up demonstrated a collective effect on weight change of –3.8 kg (95% CI 2.8–4.7). Further meta-analyses on studies limited to the USA also found clinically meaningful collective change in weight [67], with sub-analysis suggesting that automated interventions are associated with similar magnitude of weight loss to those with human elements. The evidence base is limited by publication bias [67], a paucity of trials outside the USA [66], and limited data on at-scale implementation and comparative cost-effectiveness. With the widespread adoption of smartphones [63], especially by younger generations and in low- and middle-income countries, these technologies have the potential to have an impact on the scalability and effectiveness of Type 2 diabetes prevention programmes internationally.

All interventions, including public health programmes can, through differential uptake, retention and effectiveness, both widen and narrow health inequalities; thus, research on programmes must examine how to promote equitable uptake through targeted health marketing [56], equitable retention and outcomes. The potential impact of digital interventions on health inequalities is unclear. They may increase access for rural, working age and caring-responsibility groups, but disadvantage those with limited internet access or acceptance of digital technologies, such as older populations. These issues are being considered in a major uncontrolled pilot of digital prevention interventions conducted in live service environments as part of the NHS DPP. In addition to delivery channel, programme content must also be modified where necessary to ensure accessibility for vulnerable groups, many of whom are at high risk of Type 2 diabetes, such as those with learning disabilities [68]. Other groups at high risk, such as those previously diagnosed with gestational diabetes, might particularly benefit from ensuring that there is regular surveillance in primary care [10,69]. Commissioning models can be also be designed to allow both standardization of programmes to ensure quality and reduce variation in care and adaptation to local need, as noted in the formative evaluation of the NHS DPP [70].

At scale, programmes should be based on evidence, should add to the evidence base through evaluation and should be subject to continuous improvement [21]. In the NHS DPP, for example, the service specification was written based on a commissioned systematic review [52], along with ongoing input from an Expert Reference Group. National (NICE) and International (EU-IMAGE) guidelines were used to inform programme design. This was done by analysing variations in effectiveness associated with adherence to these guidelines through subgroup analysis in the commissioned review of intervention studies [52]. A commissioned independent formative evaluation was undertaken for the NHS DPP early-phase pilots, highlighting strengths of the commissioning model, and identifying areas of focus common to behavioural programmes such as retention and quality assurance [70]. A process evaluation of the programme analysed referral and equity of access [57]. This found that referral numbers and percentage uptake were in excess of modelled values and that initial uptake of the programme reached demographic groups (e.g. black and minority ethnic groups and those resident in deprived areas) who are at greater risk of developing Type 2 diabetes and who typically access healthcare less effectively [57]. Outcomes evaluation is forthcoming. Finally, a major National Institutes of Health Research programme, the Diabetes Programme Long-term Multimethod Assessment (DIPLOMA) evaluation, has been commissioned. This provides ongoing expert input to the programme, and will provide long-term, rigorous and independent evaluation of implementation and the impact of the national programme on Type 2 diabetes incidence both at participant and at population level [71].

Data from the National Diabetes Audit in England will support NHS DPP delivery evaluation from 2018/2019, expanding from population-wide surveillance of those with diagnosed diabetes to also include those at high risk of Type 2 diabetes. Data will be systematically extracted from primary care systems for those coded with any of the descriptors consistent with high risk. The extraction has been piloted [72] and, within data quality limits, will permit longitudinal tracking of individuals at high risk. Linkage of this and service datasets from the NHS DPP will allow evaluation of targeted prevention on Type 2 diabetes incidence, longer-term incident microvascular and cardiovascular complications, and mortality. To our knowledge, this is the first national clinical audit of those at high risk that will provide such longitudinal evaluation data.

Delivery at scale requires close attention to affordability. As discussed above, at scale, affordability is a critical factor

to determine the inclusion threshold for blood tests indicating high risk. The NHS DPP impact modelling study [73] demonstrated that resources to deliver 100 000 interventions per year to the programme aligned well with NICE inclusion thresholds for non-diabetic hyperglycaemia based on the numbers already identified on general practice registers within these ranges.

A recent health economic modelling study used a Markov model to compare four prevention approaches: low-intensity lifestyle programme [group-based pragmatic programmes such as the NHS DPP (see below)], high-intensity lifestyle programmes (based on the US DPP trial), metformin, and no intervention. Low-intensity lifestyle programmes were identified as the most cost-effective strategy [62].

Prevention programmes have relatively long time frames to realise clinical and financial benefits, 12 years in the case of the NHS DPP [74]; therefore, strategic commitment to their establishment and maintenance is important. For example, in the USA, Congress authorized the Center for Disease Control to launch the US National DPP [56], whilst in the UK, the establishment of a national Type 2 diabetes prevention programme was proposed in a 5-year national NHS strategy [75]. Following initial commitment, it is important that policy makers maintain regular dialogue with implementers and researchers [21].

Conclusions

To achieve sustainability of healthcare systems, many countries are now placing greater emphasis on disease prevention. The fact that lifestyle is a major modifiable risk factor for Type 2 diabetes has caused parallel interests in interventions that empower individuals identified as at high risk of Type 2 diabetes to modify that risk beneficially, as well as broader population-level interventions that address the obesogenic environment. A remarkable international effort spanning two decades has seen the evolution of interventions for those at high risk move from efficacy trials, through effectiveness trials, to implementation at scale.

The key points identified from the present review are set out below.

1. Identification thresholds for 'high risk' in a population should be aligned to pragmatic considerations such as affordability, as long as inclusion thresholds are not so low that the cohort is diluted with too many people who are never destined to develop Type 2 diabetes.

2. The process of identification needs ongoing refinement, with specific attention to the ways that risk factor information may be combined with blood test information to improve performance.

3. Through efficacy and then effectiveness trials, we now see implementation at scale. Maximizing population-level effectiveness of behavioural interventions requires continued research focus on how to engage and retain participants, and other implementation characteristics over and above clinical effectiveness.

4. National programmes must incorporate both individual-level interventions and population-level approaches to obesity and Type 2 diabetes prevention.

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