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Addressing the Malta National Strategy for Diabetes 2016-2020 research priority areas: A scoping review

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ABSTRACT

Diabetes mellitus is one of the major reasons for morbidity in Malta. A National Diabetes Strategy launched in 2016 identified research priority areas. The aim of this scoping review was to identify and describe the research on these areas. CINAHL, MEDLINE, PsychInfo, Cochrane Database of controlled studies, Cochrane Database for systematic reviews were searched using the keywords 'diabetes' AND 'Malta'. Papers had to be relevant to the priority areas and include Maltese persons. A total of 31 papers were included. The prevalence of diabetes has been stable at 10% since the 1980s. The incidence of type 1 diabetes showed an upward trend until 2010. Genetic mutations were identified for MODY and type 2 diabetes. Excess body weight is the most important environmental risk factor, with a threshold BMI between 15 and 20 kg/m^2 to decrease diabetes risk in Maltese persons. Perceived behavioral control had the greatest impact on self-management behavior. One ehealth research project, to help primary care physicians identify those at high risk of type 2 diabetes was identified. Further research is required on all priority research areas to ensure the latest locally relevant evidence on changing trends in diabetes incidence, prevalence, genetics, risk factors, and self-management.

1. Introduction

Malta is an archipelago of three islands, Malta, Gozo and Comino. The population in 2019 was of 514,564, a rapid growth from 405,616 persons in 2006 (National Statistics Office Malta, 2020). This growth is due to an increasing influx of European Union and third country nationals seeking employment in Malta due to the expanding local job market. It is also due to the arrival of irregular migrants who mostly hail from sub-Saharan countries. Added to this is an influx of around 2.6 million tourists per year (National Statistics Office Malta, 2020). This makes Malta, which is highly urbanized and whose geographical size is 316 km^2, the most densely populated country in Europe (Azzopardi Muscat, 2018).

Malta has one of the highest life expectancies at birth in Europe, estimated at 82.5 years in 2018 (Azzopardi Muscat et al., 2014; EUROSTAT, 2020a). The healthy life years in 2018 stood at 72.7 years, second only to Sweden and well above the average of 64 years for the 27 countries of the European Union (EUROSTAT, 2020b). Notwithstanding, noncommunicable diseases are a major threat to health (Azzopardi Muscat et al., 2014).

Diabetes mellitus (DM) is one of the major noncommunicable diseases in Malta, highly prevalent since the 18th century (Savona Ventura, 2001). DM is classified by the American Diabetes Association (2020) into four main categories: type 1 diabetes mellitus (T1DM) which is caused by autoimmune destruction of the β cells and resulting in an absolute deficiency of insulin, type 2 diabetes mellitus (T2DM) which is usually caused by a combination of insulin deficiency and insulin resistance, gestational diabetes (GDM), that is diabetes in pregnant women during the second or third trimester of pregnancy in the absence of previous diabetes and other specific types of diabetes including Mature Onset Diabetes of the Young (MODY) and Late Autoimmune Diabetes of Adults (LADA).

The International Diabetes Federation (2019) estimated that about 8.3% of Maltese persons between 20 and 79 years were living with diabetes in 2019. This places Malta amongst the European countries with the highest prevalence of diabetes, making this a national health priority. For this reason, a National Diabetes Strategy was launched in 2016 covering the period between 2016 and 2020 (Calleja et al., 2016). The aim was to prioritize diabetes prevention, early diagnosis, expansion of treatment modalities, development of integrated care and prevention and postponement of complications.

This strategy also identified a number of research priority areas. These were:

- 'The local genetics of diabetes and the interaction between genetic predisposition and risk factors in the environment
- Reasons for increasing incidence of T1DM
- Motivational factors and compliance with diet and treatment regime
- National prevalence of diabetes

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- ehealth/mhealth and diabetes management' (Calleja et al., 2016, p.65)

As the deadline for the implementation of the National Diabetes Strategy 2016-2020 approaches, this review sought to identify progress made in addressing the research priority areas.

The review question was 'to what extent has research addressed the Malta National Strategy for Diabetes 2016-2020 research priority areas?'.

The objectives were to assess:

1 the extent of research carried out in Malta on the priority areas,
2 the results of this research; and
3 gaps which still need to be addressed.

2. Methods

A scoping review was chosen to meet the objectives. This is suitable in cases, such as in the present review, where the review question is broad, the research area complex and as yet unexplored; where the aim is to explore the range and characteristics of completed research; to synthesize and disseminate results to policy makers and researchers; to identify gaps and give direction for future research (Colquhoun et al., 2014; Arksey and O'Malley, 2005).

The methodological framework developed by Arksey and O'Malley (2005) as adapted by Levac, Colquhoun and O'Brien (2010) was applied. This included 6 stages; determining the research question, finding related studies, choosing studies, mapping and systemizing the data, condensing the results and presenting them.

2.1. Eligibility criteria

To be eligible for inclusion, research papers had to:

1. Include a sample of persons of Maltese nationality, living with diabetes mellitus
2. Focus on one of the following:
   - Prevalence of diabetes
   - Genetics of diabetes
   - The interaction between genetic predisposition and environmental risk factors
   - Reasons for increasing incidence of T1DM
   - Motivational factors and compliance with diet and/or treatment regimens
   - ehealth/mhealth and diabetes management
3. Be reported in English or Maltese, the two official languages of Malta.

In view of the broad terms used in some priority areas, in particular on motivational factors and compliance, papers reporting related concepts, such as self-care, knowledge of diabetes self-management and patient behavior were also included.

2.2. Information sources

The aim of the literature search was to ensure the comprehensive identification and inclusion of relevant published and unpublished papers (Arksey and O'Malley, 2005). With this in mind, the following databases, believed to be the most relevant, were searched: CINAHL, MEDLINE, PsychInfo, Cochrane Database of controlled studies and the Cochrane Database for systematic reviews. A manual search of the Malta Journal of Health Sciences, the Malta Medical Journal and the Malta Medical School Gazette was carried out. The University of Malta Open Access Repository was searched for any unpublished papers or conference proceedings. The search covered the earliest date to the 12th of February 2020 and was updated in September 2020.

2.3. Search strategy

The Boolean phrase 'Diabetes AND Malta' with the keywords present in any part of the paper was used. The following limiters were used: language English OR Maltese. No other limitations were applied.

2.4. Study records

2.4.1. Data management

The search was carried out by one individual (RS). The papers were saved to a bibliographic software database (RefWorks). Following importation of all 'hits' from the databases, duplicates were removed.

2.4.2. Selection process

The title and abstract of the retained papers were read and checked against the inclusion and exclusion criteria. Those which fit the latter, or whose focus was not clear, were retained in the next step (Arksey and O'Malley, 2005).

At this stage, the full text of the retained papers was downloaded onto a computer. The papers were read in full against the inclusion/exclusion criteria; those which matched these criteria were retained.

2.4.3. Data collection process

The retained papers were read and data from each was extracted.

2.4.4. Outcomes and prioritization

The outcomes which were recorded were the number of papers addressing each priority area in the National Diabetes Strategy 2016-2020, the results of the research and gaps for future research work.

2.5. Data synthesis

Data was synthesized using a narrative approach, in view of the heterogeneity of the studies which did not allow a meta-analysis.

3. Results

3.1. Results of the literature search

As seen in Fig. 1, the database search resulted in 264 'hits'. Ten other papers were identified following a bibliographic search of these papers. Following removal of duplicates, 274 papers were screened on the basis of their title and abstract against the inclusion and exclusion criteria. This resulted in the retention of 126 papers which were screened on the basis of their full-text. A total of 31 papers were retained; 95 were excluded. The main reason for exclusion was that the papers did not address the topics identified in the Maltese Diabetes Strategy (Calleja et al., 2016); most focused on diabetes complications, their prevention or management, which whilst very important from a clinical perspective, was not included in the Maltese National Diabetes Strategy (Calleja et al., 2016).

The retained papers were classified according to the research theme they addressed.

3.2. The national prevalence of diabetes

The estimates of prevalence of diabetes have varied over the years (Table 1). Zammit Maempel (1965, 1968) reported the highest estimated prevalence rate at 19.9%. This dropped to 7.7% in Katona et al.'s study (1983) and subsequently rose to 10% in Schranz's (1989) study. The European Health Examination Survey, a small pilot study carried out in 2010 reported that 9.8% of persons over the age of 18 years had diabetes (Directorate for Health Information and Research, 2010). This figure remained unchanged in the study by Cuschieri et al. (2016).

Table 1
The prevalence of Type 2 Diabetes and associated risk factors in Malta.

Author (Date)	Study methods	Criteria for identifying diabetes	Results
Zammit Maempel (1965)	Pilot survey in 1964	Glycosuria/non-glycosuria	513 (8.9%) had glycosuria
Zammit Maempel (1968)	6579 persons - 87.5% response (n=5757)	OGTT with fasting blood glucose or 2 hour post 50 g glucose load of 100mg/100ml;	5244 (91.1%) did not have glucosuria
	From urban (Floriana) and rural area (Gharghur, Madliena, Bahar ic-Caghaq)	At least one other figure for $\frac{1}{2}$ hr, 1hr, 1 $\frac{1}{2}$ hr post-glucose load exceeded 150 mg/100 ml	70.1% (277) of those with glycosuria
	324 with glycosuria		15% (59) those without glycosuria had diabetes mellitus
	And 392 without glycosuria submitted to OGTT test Physical test Questionnaire		Overall prevalence of DM 19.9% Clinical pattern: • 97.1% after age of 30 years • Peak age at onset 50-54 years • Incidence increased with age • Incidence of diabetes among glycosurics higher in females than in males at all age groups by about 10% • 60.4% (171) of diabetics overweight or obese vs. 44.1% of non-diabetics • Gave history of overeating • Gave history of occurrence in siblings, ancestors, offspring more than in nondiabetics • Heavy manual activity less common in diabetics (10%) than non-diabetics (42.7%)
Katona et al. (1983)	Phase I and II of prospective cohort study	OGTT with 75g glucose load.	IGT: 5.6%
	Phase I relevant	Capillary glucose sample and urine sample taken.	Diabetes: 7.7%
	Epidemiological study covered Jan-March 1981	WHO 1980 criteria used.	(1.8% newly diagnosed' 5.9% previously diagnosed).
	Population at time of study 310,000	Diabetes present if blood glucose	• Persons above 45 years more likely to develop diabetes; bimodal distribution with peaks at 45-49 years and 75+ age group.
	1100 households randomly selected from electoral register.	>120 mg/dl fasting	• Females more likely to develop diabetes
	1098 agreed to participate: 3040 persons over 15 years of age	>199 mg/dl two hours post load	• Males more likely to develop IGT and risk increases with age
	Excluded those with fasting glucose >300mg/dl	IGT	• Nearly all had a family history of diabetes
	Final sample size 2945	Normal fasting levels 140-199 mg/dl two hours post load	• Obesity most strongly linked to diabetes • 61% males and 67% of females were overweight/obese.
		Questionnaire Physical examination: BP, weight, skinfold thickness	
Schranz (1989)	6 year prospective cohort study as part of WHO National Diabetes Programme	WHO 1985 recommendations for OGTT	Age standardized prevalence rates 35-69 years
Follow-up of Katona et al (1983)	1422 (66.8% of original sample) completed study OGTT test Questionnaire Clinical examination		IGT: 13.1% Males: 12.89% Females: 13.24% Diabetes: 10% Males: 9.07% Females: 10.77% Clinical pattern • Gradually increased after age 35 years • IGT peaked at 60 years and over • Diabetes peaked at 70 years and over • Diabetes more common in females • IGT more common in males • Heredity major influence (close relatives with diabetes) • Excess body weight main environmental factor: 42% males; 31% female overweight; 20% male, 34% female obese • Mean BMI increased with age • Mean BMI increased more for women than men • Duration and age of onset of adiposity may be important • No difference with physical exercise

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Table 1 (*continued*)

Author (Date)	Study methods	Criteria for identifying diabetes	Results
Schranz et al. (1991)	2 year follow up study of 388 Maltese participants	OGTT with 75 g glucose load	• Strongest predictors of 2 hour blood glucose: age, family history, physical activity • 2 year risk of glucose intolerance (impaired glucose tolerance and type 2 diabetes) inversely related to physical activity • For those with normal glucose at start of the study, low physical activity increased risk of glucose intolerance by 2.7 times. • For those with normal and impaired glucose tolerance at the start of the study, low physical activity increased risk of glucose intolerance by 3.7 times. • Same for diabetes.
Papoz and the EURODIAB Subarea C study group (1993)	Average daily dose of insulin, biguanide or sulphonylurea in the population with diabetes		Prevalence of 4.7% of diabetes 20% difference to previous studies on diabetes
Schranz (1994)	Prescribed average daily dose of each type of anti-diabetic drug (insulin, biguanide, sulphonylurea)	Quantity of drugs consumed from government and private pharmacies	Prevalence of diabetes: 5.22%
	Random representative sample of 1444 patients attending public health centres and private practitioners.	Same formula applied as for EURODIAB study (1993)	12% lower when compared to population based epidemiological studies.
Schranz and Savona Ventura (2002)	Longitudinal study	75 g OGTT	Normal gestational glucose tolerance: 10% abnormal glucose tolerance
Savona Ventura, Schranz and Chircop (2003)	1985: 269 pregnant women	WHO diagnostic criteria of 1985; reclassified in 1993 according to current criteria	Borderline gestational IGT: 36.4% abnormal glucose tolerance
	1993: 116 women (43.1%)	Normal glucose tolerance: <7.8 mmol/,	Gestational IGT: 66.7% abnormal glucose tolerance
	Mean age 28.7 years +/- 5.32 years	Borderline glucose tolerance: 7.8-8.5 mmol/l	Normal gestational glucose tolerance: 5.6% Diabetes Mellitus
		Impaired glucose tolerance: 8.6-11.0 mmol/l	Borderline gestational glucose tolerance: No cases of Diabetes Mellitus
		1993 criteria	Gestational IGT: 53.3% Diabetes Mellitus
		75 g OGTT	Obesity during pregnancy not related to development of glucose intolerance
		2 hour post load	In follow up period:
		IGT: 7.8-11.0 mmol/l	High BMI and high weight:hip ratio related to present abnormal glucose intolerance
		DM: >11.0 mmol/l	Hypertension related with increased prevalence of glucose intolerance
		BMI	Family history: maternal or sibling family history related to glucose intolerance
		Waist:hip ratio	Paternal family history not related.
The DECODE/A study group (2003) Secondary analysis of pre-existing data	Population based studies carried out after 1980 11 European studies	1990 WHO criteria based on standard 75g OGTT	Higher prevalence for diabetes in India and Malta compared to Japan, China and Europe Increase in prevalence of diabetes in Maltese and Indian populations at lower BMI between 15 and 20 kg/m^2 compared to 25 kg/m^2 in Europeans
For Maltese study: Schranz et al. (1991)	1 Maltese study		Association between age and prevalence of diabetes was higher for the Indian subjects followed by the Maltese
	3 Indian studies		In Maltese prevalence of diabetes increased with BMI in men but not in women. No difference in other ethnicities.
	2 Chinese studies 3 Japanese studies 14240 men and 15129 women aged 30-89 years		
Directorate for Health Information and Research (2012)	Stratified random sample based on age, gender and locality of residence.	Health questionnaire on health status and demographic variables.	Diabetes
European Health Examination Survey 2010	N=400; 221 participants	Health examination: weight, height, blood pressure, blood tests including blood glucose	9.8% of sample
	18 years and above	Diabetes identified if FBG >7.0mmol/l, RBG >11.1 mmol/l	
	Data collected in 2010		9% male 10.7% female Obesity more common in women Prevalence rises after age 40 Highest prevalence in 60+ age group.

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Table 1 (*continued*)

Author (Date)	Study methods	Criteria for identifying diabetes	Results
Cuschieri and Mamo (2015), Cuschieri et al. (2016)	Stratified random sample from official register: included foreigners who had been in Malta for 6 months.	Questionnaire based assessment	10.39% (95% CI: 9.47–11.38) suffered
Cuschieri et al. (2016)	18-70 years old Stratified by age, gender and town. Sample of 4000 taken Final sample: 3974; 1998 males, 1949 females	Physical assessment (BP, height, weight, waist-hip ratio) Biochemical measurement: FBG, lipid profile, OGTT	from diabetes, among which 6.31% (95% CI: 5.59–7.11) were previously known diabetics and 4.08% (CI: 3.50– 4.74) were newly diagnosed. Persons with diabetes were either overweight or obese (92.20% CI 95%: 89.16–94.45). Persons under 55 years were predominately obese (50% CI 95%: 40.56–59.44) or overweight (46% CI 95%: 36.88–55.70), with only 4% (CI 95%: 2–8.9) having normal weight. Adults ≥55 years were of normal weight (9% CI 95%: 6.37–12.50) with 57% (CI 95%: 51.50–61.61) of these found obese and 34% (CI 95%: 28.59–39.13) found to be over weight (p = 0.001).
Cuschieri et al. (2019)	Same as Cuschieri and Mamo (20015) above National representative health examination survey	Different smoking habits: Current – smoke one or more cigarettes per day Former smoker – stopped at least 1 year ago Passive smoker regular exposure to cigarettes for more than 1 hour per day Non smoker	Prevalence of smoking: Smokers: 24.3% Former smokers: 19% Passive smokers: 27.24% Former smoking independently associated with impaired fasting glucose and type 2 diabetes (Odds Ratio 1.67; 95% CI 1.10-2.54; p=.02) compared to nonsmokers

N.B. OGTT: Oral glucose tolerance test; FBG: fasting blood glucose; RBG: random blood glucose; BP: blood pressure; BMI: body mass index; CI: confidence interval; IGT: impaired glucose tolerance; DM: diabetes mellitus.

Papoz and the EURODIAB Subarea C Study Group, (1993) and Schranz (1994) used a proxy measure for diabetes prevalence. The proxy measure utilized was the prescribed average daily dose of antidiabetic medication (at the time of this study these were insulin, biguanide and sulphonylurea). They identified a much lower prevalence of diabetes in Malta than that reported in studies using direct measures, 4.7% and 5.22% respectively.

3.3. Genetics

Three papers focused on the genetics of diabetes within the Maltese population. Two papers focused on gene mutations associated with MODY; the third paper focused on gene mutations associated with T2DM. All three utilized a case study design.

3.3.1. Genetic mutations associated with MODY

Pace et al. (2018) report on a woman with obesity, diabetes and diabetic nephropathy in the absence of renal cysts. They identified a rare mutation in exon 8 of HNF1β (c.1580G>A, NM-004583, p.Arg527Gln), never previously reported in Malta and characteristic of Southern European people. This mutation was subsequently found in another unrelated woman screened for MODY.

Pace et al. (2019) report on a case study of a Maltese man and his three children. These presented with diabetes at a young age, a strong family history of diabetes without ketoacidosis, differing need for insulin, the presence of C-peptide enzyme, no obesity, and the absence of anti-islet antibodies. The females presented with GDM which did not resolve following delivery. Genetic testing identified an HNF1α mutation in exon 4, indicating MODY 3, which was not previously reported in Malta. This mutation is characteristic of Northern European populations.

Pace et al. (2019) reported that further research was being carried out with Maltese families with a high likelihood of MODY, and a cohort of women with GDM. An abstract for a paper presented at the European Society of Endocrinology in September 2020 was identified (Pace et al.., 2020). The full text was however not available and full details of the study are not presented here. The study included 30 Maltese women with GDM and first-degree family members with non-autoimmune diabetes. Three pathogenic mutations were identified; a nonsense mutation in *GCK*, an insertion-frameshift at a mutational hotspot in *HNF1A* and a missense substitution in *ABCC8*.

3.3.2. The genetics of GDM and T2DM

Three Maltese women with severe GDM were followed at 4-7 years post-partum to identify any underlying genetic differences associated with development of impaired glucose tolerance (IGT) or T2DM (Abou-Hussein et al.., 2011). At 4-7 years, one woman had T2DM, one had IGT whilst the third had normal glucose tolerance. The focus was four single nucleotide polymorphisms (SNPs), SLC2A2 (rs5393A/C), FTO (rs9939609A/T), PCK (rs2071023C/G) and CDKAL1 (rs10946398A/C). The results showed that the woman with T2DM had homozygous mutant SNPs, the woman with IGT had heterozygous mutant SNPs. The woman with normal glucose tolerance had a wild type for SLC2A2(rs5393A/C), and was heterozygous for two SNP genes, with one mutant and one wild type SNP gene.

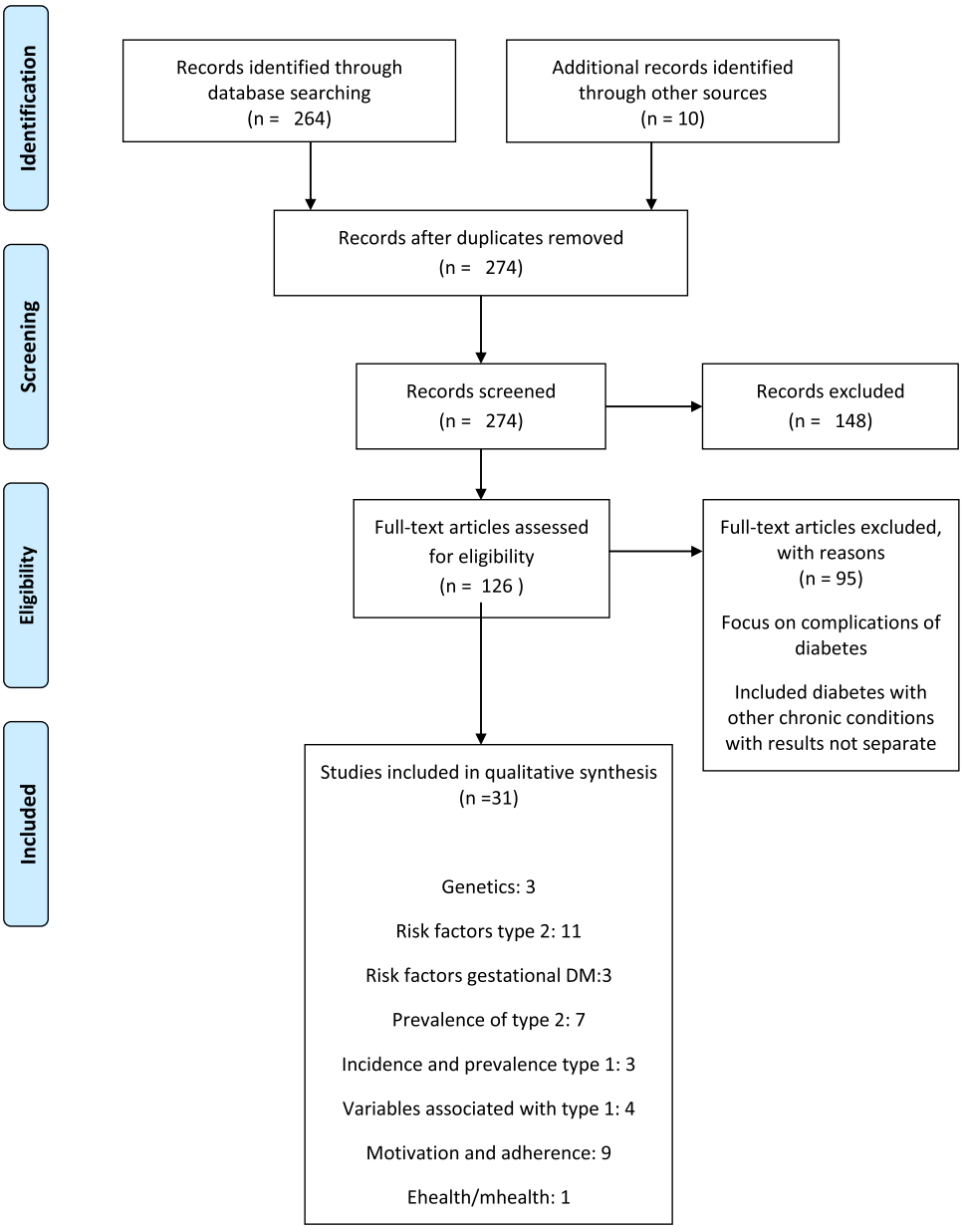

Fig. 1. Prisma flow diagram.

3.4. The interaction between genetic predisposition and environmental risk factors

Several studies (n=11) explored the environmental risk factors associated with IGT, GDM and T2DM. None explored the possible interaction between genetic predisposition and environmental risk factors.

3.4.1. Studies focusing on risk factors of T2DM

The studies exploring risk factors for T2DM are summarized in Table 1. The earliest studies were carried out in the mid-1960s. Several identify an association between familial history and T2DM (Zammit Maempel., 1965; Zammit Maempel., 1968; Katona et al., 1983; Schranz., 1989). Some identify a link for maternal or sibling, but not paternal family history (Savona Ventura et al., 2000; Savona Ventura et al., 2001; Schranz and Savona Ventura, 2002).

Of the environmental factors, body weight was the most important, with all studies identifying overweight and obesity as being most strongly associated with diabetes (Zammit Maempel., 1965; Zammit Maempel., 1968; Katona et al., 1983; Schranz., 1989; Schranz and Savona Ventura, 2002). The DECODE/A study group (2003) compared the relationship between weight and diabetes on the basis of ethnicity through secondary analysis of nationally representative epidemiological studies. This study included that by Schranz et al. (1991). Diabetes prevalence was higher in India and Malta, when compared to Europe, China and Japan. The increased prevalence occurred for Maltese participants at a BMI between 15 and 20 kg/m^2, compared to a higher BMI of 25 kg/m^2 in Europeans (The DECODE/DECODA Study group, 2003).

Whilst Schranz (1989) reported no significant association between physical activity and diabetes, Zammit Maempel (1965, 1968) reported that persons with diabetes were less likely to be engaged in heavy work. A 2-year longitudinal study identified that those with normal blood glucose at baseline were 2.7 times more likely to develop IGT if they were not physically active, increasing to a 3.7 higher risk for those with IGT at the start of the study (Schranz et al., 1991).

A longitudinal study of women (Table 1) identified an association between IGT during pregnancy and IGT and diabetes eight years later (Schranz and Savona Ventura, 2002). Cuschieri et al. (2019) identified an association with smoking, with those who quit smoking 1 year or ear-

Table 2
Gestational Diabetes Impaired Glucose Tolerance, Gestational Diabetes and associated risk factors in Malta.

Author (Date)	Study methods	Criteria for identifying diabetes	Results
Savona Ventura, Azzopardi and Sant (2000)[l]	20,073 deliveries in public hospital in Malta Pre-existing DM excluded GDM: n=106 (0.53%) G-IGT: n=131 (0.65%)	Not reported in paper.	Risk factors for GDM Older than 35 years (x2.8RR) High BMI with: Short stature (x1.5RR) Obese (x3.0RR) Multiparous (x4.1RR) History of previous caesarean section (x2.6RR) G-IGD risk factors: No statistically significant risk factors identified.
Savona Ventura, Schranz and Chircop (2001)	269 Maltese pregnant women attending antenatal clinics in a large general Maltese hospital Non-Maltese and those with diagnosed GDM excluded 2 women identified during study and excluded	75g OGTT at 34 weeks pregnancy WHO 1985 criteria G-IGT: 2hr blood glucose of 7.8 mmol/l GDM: 2 hr blood glucose >11mmol/l	Risk factors for GIGT • Aged more than 35 years (x3.95 RR) • Previous early pregnancy loss (x5.47 RR) • Maternal history of carbohydrate metabolism problems (x2.54 RR) • Post-prandial glycosuria in the third trimester (x2.14 RR) • More likely to require operative delivery including caesarean section
Savona Ventura and Chircop (2003)	388 records: 162 women diagnosed with GDM and with information on birth weight 250 controls	75g OGTT GDM 2hour post load >8.6mmol/l Birth weight: Low: 1000-2000g High: >4500g	U-shaped statistically significant distribution: Women with low birth weight and high birth weight at higher risk of GDM. Those with GDM maternal history of diabetes. No difference for paternal history.

N.B. GDM: Gestational Diabetes Mellitus; OGTT: Oral Glucose Tolerance Test; RR: relative risk; G-IGT: Gestational Impaired Glucose Tolerance.

lier, having a higher risk of diabetes than those who had never smoked. No association was found for current smokers or passive smokers (Papoz and the EURODIAB Subarea C Study Group, 1993).

3.4.2. Studies focusing on the risk factors for GDM

Three studies (Table 2) focused on the risk factors for the development of GIGT and GDM (Table 3.2). One identified the risk factors for GDM to include age over 35 years, a high BMI, with short stature and obesity, multiparity and a history of caesarean section (Savona Ventura et al., 2000). No risk factors were identified for GIGT. A later study identified similar risk factors, that is being older than 35 years and the need for a caesarean section (Savona Ventura et al., 2001). It also identified a maternal history of diabetes, previous early pregnancy loss and glycosuria post-prandially in the third trimester. In addition, Savona Ventura and Chircop (2003) reported that women who had extremes in birth weight were at an increased risk of developing GDM later on in life.

3.5. Reasons for increasing incidence of T1DM

The following sections focus on studies which researched the incidence and prevalence of T1DM and environmental risk factors.

3.5.1. The incidence and prevalence of T1DM amongst children and young adults

Three studies explored the incidence of T1DM in children and young adults in Malta (Schranz and Prikatsky., 1989; Schranz, 1998; Formosa et al., 2011). These showed an increased incidence between 1980 and 2010 (Table 3). Incidence rose from 13.3 per 100,000 per year between 1980 and 1987, to 21.86 between 2006 and 2010 (Schranz and Prikatsky, 1989; Formosa et al., 2011). Data beyond 2010 is unavailable. Whilst Schranz and Prikatsky (1989) reported a minimal increase in yearly incidence, Formosa et al. (2011) reported an exponential statistically significant increase between 2006 and 2010, rising from 16.14 to 31.6 per 100,000 with a yearly increase of 21.8%.

Schranz and Prikatsky (1989), the only to report prevalence rates in Malta, reported a prevalence of 110.3 per 100,000 children and young adults with a higher prevalence of 126.2 for females, compared to 95.3 for males. Data beyond 1987 is unavailable.

3.6. Motivational factors and compliance with diet and/or treatment regimens

Nine studies focused on patient awareness and knowledge of diabetes, self-care behavior and adherence to treatment.

Formosa et al. (2008) reported that offering persons with diabetes an educational programme does not result in knowledge improvement. Sapiano et al. (2012) conversely reported improved knowledge following an educational programme on preconception care offered to women with T1DM. Formosa and Muscat (2016) and Cuschieri and Grech (2019) both report no association between knowledge or awareness of T2DM and its management or actual behavior.

Gatt and Sammut (2008) and West et al. (2018) sought to explain the reason for self-care management and behavior among Maltese persons with T2DM. Gatt and Sammut (2008) report that perceived behavioral control was the strongest predictor of behavior. The results showed that the aspects over which persons felt they had most control was medication taking. Participants reported least perceived control over diet and exercise. West et al. (2018) reported that medication adherence is dependent on the person's beliefs that the medication is necessary, balanced against beliefs about any ill-effects.

Table 3
Incidence and Prevalence of T1DM in the Maltese Islands 1980-2010.

Author/s	Time frame covered and age range	Mean age and sex standardized incidence rate per year per 100,000	Incidence rate by age			Number and Incidence rate by gender/100,000	Prevalence per 100,000	Prevalence by gender per 100,000		
			0-4 year	5-9 years	10-14 years	Male	Female	Male	Female
Schranz and Pritkasky (1989)	1980-1987	13.3 (95% CI 11.6-15.0)	N/A	N/A	N/A	n=52	n=65	110.3 (95% CI 90.5-130.1)	95.3 (95% CI 77.3-113.3)	126.2 (95% CI 105.4-147.0)
	0-19 years					N/A	N/A			
Schranz (1998)	1990-1996	15.6 (95% CI 11.2-20.1)	N/A	N/A	N/A	12.9-15.5	14.7-15.7	N/A	N/A	N/A
	0-14 years									
Formosa, Calleja and Torpiano, (2011)	Jan 2006-Dec 2010	21.86 2006: 16.14 (95% CI 11.28-21.02)	21.7 (95% CI 8.9-34.5)	30.4 (95% CI 9.8-51.0)	16.1 (95% CI 10.9-21.4)	n=41	N=40	N/A	N/A	N/A
	0-14 years	2010: 31.6 (95% CI 17.7-45.4)								

3.7. ehealth/mhealth and diabetes management

One paper on ehealth/mhealth was identified (Azzopardi et al., 1995). This evaluated the sensitivity and specificity of a computer-based patient questionnaire named 'Għalik' (For You) which sought to screen patients for diabetes risk at primary care level, identify those at high risk and provide protocols for follow up to be applied (Azzopardi et al., 1995). The sample included a group of 128 recently diagnosed persons with T2DM, and a control group of 320 persons. The latter had an oral glucose tolerance test (OGTT) prior to the study. This electronic screening tool demonstrated good sensitivity and specificity in identifying those at high risk of diabetes.

4. Discussion

The following sections provide a discussion on the research gaps identified and recommendations on ways forward in clinical practice and future research.

4.1. The national prevalence of diabetes

Regular estimation, at a national level, of the prevalence of diabetes and its associated risk factors is important to allow the development of evidence-based strategies for diabetes prevention (Cuschieri et al., 2016). Regular population based, national studies on the prevalence of diabetes in Malta are lacking, with a hiatus of 26 years in research between 1989 (Schranz., 1989) and 2016 (Cuschieri et al. 2016; Cuschieri and Mamo, 2015; Cuschieri et al., 2016). The last point for a national study was 2016. It is recommended that research on the prevalence of diabetes and its risk factors should be carried out at least every five years to allow development of suitable strategies to prevent diabetes and evaluation as to whether these are effective or not (Cuschieri and Mamo, 2015). The five-year period is suggested as the European Health Interview Examination is carried out every five years and would provide a benchmark for comparison of the results to those in other European countries.

The study by Katona et al. (1983) reported a prevalence of diabetes in Malta of 7.7% (Katona et al., 1983). This rose to 10% within a 6-year span, in Schranz (1989). The latter, the European Health Examination Survey (2010) and Cuschieri et al. (2016), all estimate the prevalence of T2DM in Malta as being around 10% (Directorate for Health Information and Research, 2010). This indicates that whilst there was a rise in the prevalence of T2DM between 1983 and 1989, this has remained stable over the past 31 years. This trend is contrary to the rise reported in other countries. This may indicate that Maltese persons are more aware of the importance of prevention of diabetes or prevention strategies, such as weight reduction and exercise programmes, offered by the health promotion department are being effective.

Whilst the prevalence of T2DM has remained stable over a significant number of years, it still remains high compared to the EU average of 6.9% (EUROSTAT, 2014). Besides the effects on morbidity, mortality and the psycho-social impact of living with diabetes, this has a significant cost burden on the country. It is estimated that this cost is about €29,159,217 annually, contributing to 3.65% of the total health expenditure for Malta (Cuschieri et al. 2016). It is moreover predicted that due to an ageing population in Malta, the prevalence of diabetes will rise, with an estimated 25,071 living with diabetes in 2050, compared to 19,558 in 2016 (Cuschieri et al. 2016). This means that urgent action is needed.

4.2. Genetics

4.2.1. Genetic mutations associated with MODY

There is a total of 14 MODY subtypes (Baldacchino et al., 2020); two of these have been identified in research carried out in Malta to date. Pace et al. (2018, 2019) in their case studies identified missense

mutations in Hepatocyte Nuclear Factor 1β (HNF1β) and Hepatocyte Nuclear Factor 1A (HNF1A) as underlying MODY (Pace et al., 2018; Pace et al., 2019). This was the first time these rare mutations were identified within the Maltese population.

The authors suggest this indicates the need for research on the genetic epidemiology of MODY in Malta in view of the several founder effects expected. These founder effects are the result of the historical influx of colonizers from various regions, depopulation and repopulation of the islands, as well as migration patterns (Pace et al., 2018; Pace et al., 2019; Baldacchino et al., 2020). The further research presently being carried out by Pace et al. (2019) is encouraging and should contribute to the knowledge of the genetics of MODY in Malta.

4.2.2. The genetics of gestational and type 2 diabetes

The only study on the genetics of T2DM focused on the severity of problems with glucose metabolism in women post-partum and single nucleotide polymorphisms (SNPs) mutation (Abou-Hussein et al., 2011). This showed that since clinical presentation was the same in all three women, prediction based on risk factors alone was inadequate. Genetic testing is required to identify those at high, low or negligible risk. This would allow prompt lifestyle changes and early medical intervention.

The genetics of T2DM is an area where research is lacking locally. T2DM can be prevented or attenuated if a genetic predisposition is identified, through the removal or manipulation of environmental factors, such as normal weight maintenance (Cuschieri, 2019).

Interestingly, several studies identified a link between post-gestational IGT and DM and maternal but not paternal history of DM (Savona Ventura et al., 2000; Savona Ventura et al., 2001; Schranz and Savona Ventura, 2002; Savona Ventura et al., 2003). This indicates that whilst a genetic predisposition to developing IGT and DM does exist, this could be moderated by the interuterine 'milieu interieur' of the foetus of mothers with abnormal glucose metabolism (Savona Ventura et al., 2000; Savona Ventura et al., 2001; Schranz and Savona Ventura, 2002). Nutritional deprivation or excess in utero may alter the development of the foetal pancreas, as well as the response to insulin, subsequently resulting in DM during adulthood (Savona Ventura and Chircop, 2003). This suggests that education and follow up of pregnant women is important to ensure optimal nutritional intake to prevent T2DM in the child in the future.

4.2.3. Genetics of T1DM and LADA

Research on the genetics of T1DM and LADA is absent locally. Seventy-three different genes are possibly related to the pathogenesis of T1DM (Yahaya and Salisu., 2020). The search for the genetic cause for T1DM is not a simple one, as it is caused by an interaction of different genes which suppress or overexpress each other's function (Yahaya and Salisu., 2020). The latter, together with environmental triggers, may initiate T1DM (Yahaya and Salisu., 2020). Whilst these studies are complex, they should be encouraged, as the future goal is that of providing tailored care, targeting the mechanisms set in motion by the genes involved, rather than the current generic approach to management of T1DM (Yahaya and Salisu., 2020).

Genetics has an important part to play in influencing the age at which T1DM occurs (Redondo and Concannon, 2020). The highest prevalence of T1DM in Malta was for the 5-9-year-old age group, followed by the 0-4-year-old age group (Redondo and Concannon, 2020). Young age at diagnosis indicates a stronger genetic influence, which appears to be the case for the Maltese population (Redondo and Concannon, 2020).

LADA is less associated with the genes associated with T1DM and more with the genetic loci for T2DM (Redondo and Concannon, 2020). Further research is necessary to establish the genetic link for LADA in the Maltese population.

4.3. The interaction between genetic predisposition and environmental risk factors

4.3.1. Studies focusing on risk factors of T2DM

A good number of studies have focused on the risk factors for T2DM in Malta. There remains however a dearth of research on the interaction between the genetic predisposition for T2DM and environmental risk factors. This means that this is an area ripe for investigation.

The most strongly associated environmental risk factor is excess body weight. Whilst not all overweight or obese persons develop diabetes, adiposity starts off a process of metabolic changes which cause the onset or progression of insulin resistance in predisposed individuals (Cuschieri et al., 2016). There can therefore be no strategy to decrease the prevalence of diabetes in Malta, without a parallel strategy to decrease obesity (Cuschieri et al., 2016). The DECODE/A Study Group (2003) identified that Maltese persons developed diabetes at a lower BMI than other Europeans, with the cut-off point being between 15 and 20 kg/m^2 compared to 25 kg/m^2 (The DECODE/DECODA Study group, 2003). This indicates that lower weight thresholds need to be applied in Malta, possibly due to a tendency to greater central obesity in persons of Maltese origin (The DECODE/DECODA Study group, 2003).

IGT during pregnancy was strongly associated with later development of IGT and T2DM in women (Schranz and Savona Ventura, 2002). It is therefore important to follow up these women to identify possible DM at an early stage, preventing its complications. Women with a history of IGT during pregnancy should be encouraged to maintain a normal BMI.

A relationship between smoking cessation and glucose intolerance was reported (Cuschieri et al., 2019). This may be due to consumption of high sugar and fatty snacks by smokers as they seek to quit smoking (Cuschieri et al., 2019). This suggests that smoking cessation programmes need to include a nutritional and weight management programme as part of their educational package (Cuschieri et al., 2019). Notwithstanding the risk of glucose intolerance, the benefits of quitting smoking outweigh the risks (Cuschieri et al., 2019).

The association between physical activity and diabetes prevention appears to be mixed. Schranz et al.'s (1991) study shows a strong negative relationship between physical activity and glucose intolerance (Schranz et al., 1991). The longitudinal nature of this study makes the evidence for a likely association between physical activity and glucose intolerance strong. Physical activity should therefore continue to be promoted as part of a healthy lifestyle.

4.3.2. Risk factors for GDM

A number of the risk factors for GIGT and GDM, such as weight at birth, maternal history of diabetes and previous caesarean section are not within the individual's control. Some, however, are. Two studies for example, identified the woman's age as being a risk factor (Savona Ventura et al., 2000; Savona Ventura et al., 2021). This is an important finding since women are delaying pregnancy, mostly due to study and career plans, delayed marriage, effective contraception and increased life expectancy (Collict et al., 2018). The average age for Maltese women to give birth to the first child is 29 years (Pace., 2019). The number of women in Malta who gave birth between 35 and 40 years of age increased from under 400 in 2005 to 700 in 2014 (Debono, 2019). This trend will likely cause an increase in the number of women with GDM in the future and women of childbearing age should receive counselling to make them aware of the risk associated with delaying pregnancy (Collict et al., 2018). Another risk factor within the woman's control is body weight since high BMI was associated with GDM and GIGT (Collict et al., 2018). Efforts should be made by women seeking to conceive and by women during pregnancy to maintain normal weight (Collict et al., 2018).

Table 4
Studies focusing on psychosocial factors and diabetes management.

Author (Date)	Concept explored and Study Design	Sample size and Method	Instrument Used	Results
Formosa et al. (2008)	Diabetes Education effectiveness Quasi-experimental Design	Intervention group 50 persons with type 2 diabetes receiving educational programme Control 50 persons with type 2 diabetes not receiving programme All Maltese 45-65 years Non-random sample	Diabetes Knowledge Questionnaire (Meadows et al. 2000) HbA1c Lipid profile Weight Blood pressure Taken at first interview and 3 months later	No statistically significant difference between intervention and control group found in any outcome variable.
Gatt and Sammut (2008)	Attitudes, social norms, behavioural control and intent to perform self-care behavior and actual self-care behavior 2 stage cross-sectional survey design	200 Maltese persons, 50 years and over, diagnosed with diabetes for at least 6 months. Randomly selected from Diabetes Register n=100 (50% response rate) 39% male; 61% female	Scale developed to measure attitudes, social norms, behavioural control and behavioural intent by authors 1 week later Summary of Diabetes Self-Care Activities	Most positive attitude to foot care; most negative to medication taking Perceived social norm highest for diet; lowest for foot care Perceived behavioural control highest for medication taking; lowest for exercise, dietary adherence, blood glucose testing Highest intention to perform behavior for medication taking and foot care Actual behaviours performed most consistently medication taking and foot care Behavioral control most predictive of behavioral intent and actual behavior.
Sapiano et al (2012)	Level of knowledge and awareness of preconception care in persons with type 1 diabetes Pre-post interventional design (pre-experimental)	Convenience sample of 37 persons with type 1 diabetes mellitus 12-30 years of age. Completion rate 70% (n=26)	Educational intervention delivered to whole sample Self-administered questionnaire	Before intervention 26 reported no knowledge on preconception care. 11 who did reported source of knowledge was diabetologist (n=8) Statistically significant increase in knowledge following intervention.
Bartolo, Mizzi and Formosa (2013)	Foot care behavior in persons with type 2 diabetes	Convenience sample of 60 persons attending foot care clinic 30: 45-64 years 30: >45 years	Nothingham Assessment of Functional Footcare (Lincoln et al 2007)	Mean score: 45-64 years 55.43% >65 years 54.73% No statistically significant difference Suboptimal foot care
Bason, Serracino Inglott and Azzopardi (2015)	Motivation, patient knowledge regarding lifestyle modification in type 2 diabetes	Convenience sample 200 persons with type 2 diabetes 100 from diabetes clinical in large hospital; 100 from three community health centres 193 completed study Mean age 65 years	Questionnaire Fasting blood glucose Total:high density lipoprotein cholesterol HbA1c Triglycerides	67% visiting health centres participated in physical activity; 33% visiting hospital participated in physical activity 29.3% always follow nutritionist's diet plan. HbA1c and fasting blood glucose lower for those visiting health centres
Formosa and Muscat (2016)	Diabetes knowledge and self-care practices Survey design	Convenience sample 50 persons with type 2 diabetes from primary health care clinics 21 men 29 women Primarily responsible for own management	Diabetes knowledge questionnaire Summary of Diabetes Self-Care Activities	Mean Diabetes knowledge: 14.4 out of 24 Mean Self-Care Activities: 2.89 out of 7 Deficit in number of critical aspects of diabetes No significant relationship between knowledge and self-care behavior Significant relationship between knowledge and diet. Educational level and age significantly related to knowledge and self-care.

(*continued on next page*)

Table 4 (*continued*)

Author (Date)	Concept explored and Study Design	Sample size and Method	Instrument Used	Results
Formosa et al. (2018)	Adherence to prescribed footwear and reasons for nonadherence where present	Purpose sample of 12 persons with type 2 diabetes prescribed therapeutic footwear for at least 6 months	Unstructured interview	Only one person consistently used therapeutic footwear.
	Exploratory qualitative design with Interpretative Phenomenological Analysis	6 males		Most used footwear only outside.
		6 females		Reasons for non-adherence: Too heavy/uncomfortable/bulky Too warm Not elegant enough for females Understood importance of use
West, Borg Theuma and Cordina (2018)	Adherence as a result of beliefs in relation to 'necessity' for and 'concerns' about the medication.	Patients confirmed with asthma, cardiovascular disease, diabetes (latter reported here).	Tool for adherence behavior screening	Diabetes patients were more nonadherent that those with cardiovascular disease or asthma.
	Cross-sectional survey	110 persons with diabetes from large general hospital Convenience sample	Belief about medicines questionnaire - specific	Adherence increased as necessity beliefs increased and concern beliefs decreased.
Cuschieri and Grech (2019)	Diabetes awareness and dysglycaemia	155 participants with impaired fasting blood glucose (FBG 5.6-6.99mmol/l)	Diabetes Awareness QuestionnaireOGTT	Good awareness was present on risk factors for DM, symptoms and complications, ways to monitor DM.
	Cross-sectional survey design	Median age 56 years	Weight and Height, BMI	Majority obese, with elevated B.P. and raised blood glucose levels.
		Convenience sample	B.P.	Being female, ageing, non-smoker and having a family history of diabetes was significantly positively correlated with diabetes awareness.
			Highest education level District of residence First degree relatives with history of DM Alcohol intake in past 12 months Smoking in past 12 months	

4.4. Reasons for increasing incidence of T1DM

4.4.1. The incidence and prevalence of type 1 diabetes amongst children and young adults

Data on the incidence of T1DM is lacking, with the latest study having been conducted in 2010 (Formosa et al., 2011). The incidence in 2010 was 21.86 per 100,000 of the Maltese population. The DiaMond project compared the incidence of T1DM in several countries worldwide and categorized the incidence as very low (<1/100,000 per year), low (1-4.99/100,000 per year), intermediate (5-9.99/100,000 per year), high (10-19.99/100,000 per year), and very high (> or =20/100,000 per year) (Karvonen et al., 2000). This placed the incidence of T1DM in Malta, at the time, in the very high bracket.

The data for 2010, showed a sharp consistent increase in the incidence of T1DM in Malta since the earlier studies in the 1980s (Schranz and Prikatsky, 1989; Formosa et al., 2011). This suggests that the time is ripe for a population-based study on the incidence of T1DM, to assess whether this trend has been sustained over the past ten years.

4.4.2. Variables associated with incidence of T1DM

The disparity in incidence of T1DM across countries is attributed to environmental factors, but knowledge on these is very limited (Karvonen et al., 2000). The studies carried out in Malta suggest that peak occurrence of T1DM occurs during the winter months. This indicates a possible link with exposure to viral diseases, more common during this time (Schranz and Prikatsky, 1989; Schranz, 1998). A number of environmental viruses have been linked to T1DM, but these are still unconfirmed (Levet et al., 2019). The strongest association is for enteroviruses, particularly coxsackieviruses B. Enteroviruses are hypothesized to interact with islet cell CAR coxsackie adenovirus receptors, expressed on the alpha and beta cells, infecting the pancreatic islet cells. The cells then launch an antiviral response, contributing to the development of T1DM (Levet et al., 2019).

4.5. Motivational factors and compliance with diet and/or treatment regimens

The studies summarized in section 3.6, clearly indicate that education, whilst resulting in improvement in knowledge and awareness of diabetes, does not result in behavioral and lifestyle change, necessary for successful self-management of diabetes (Cuschieri and Grech, 2019). A limitation of the studies which focused on educational interventions, however, was that these appeared to appraise unstructured education. Structured education has been shown to be effective in several reviews (Deakin et al., 2006; Chen and Li, 2009; Chomutare et al., 2015; Chrvala et al., 2016). Improvements in HbA1c, fasting blood glucose, body weight, blood pressure and diabetes medication need have been identified with participation in structured diabetes education programmes (Deakin et al., 2006). Despite the evidence to the effectiveness of structured education, this is as yet not available in Malta. Further research should focus on evaluating the effectiveness of structured education in the local setting, with a view of assessing whether this should be introduced as part of the diabetes services.

Gatt and Sammut (2008) reported that intent and actual behavioral change was greatest for medication taking, the behavior which requires the least effort by the individual and which has the least lifestyle impact (Gatt and Sammut, 2008). The simple act of medication taking however, involves a decisional process by the individual who may choose to adhere or not adhere on the basis of whether the concerns about the effects of the medication is balanced by its perceived need (West et al., 2018).

Behavioral change requires the complex setting into motion of the will or motivation to change one's lifestyle, as theorized in Prochaska

and DiClemente's (1984) transtheoretical model of behavioral change. Whilst not underplaying the need for educational interventions, particularly structured education, other interventions need to be introduced to support lifestyle adaptation. This includes such interventions as motivational interviewing. Motivational interviewing was reported to be effective in promoting adherence to self-care management of persons with T2DM (Safari et al., 2019).

4.6. ehealth/mhealth and diabetes management

The computer-based questionnaire 'Għalik', was the only ehealth initiative identified during this scoping review (Azzopardi et al., 1995). This initiative, showed great promise in view of the low number of false positive and false negative results, when used to identify individuals at high risk of T2DM (Azzopardi et al., 1995). It is not known whether this tool was actually put to use, having been designed for use by primary care physicians to decide on further investigation of those identified as high-risk. It is not enough for an electronic tool to be sensitive and specific; it also needs to be acceptable and feasible to use on the front line. No feasibility or acceptability studies of the 'Ghalik' computer based questionnaire were identified. In view of its good established features, it may be recommendable to further develop this tool using current technology such as an App which can be used by primary care physicians and assess its feasibility and acceptability.

A brief search for mHealth and eHealth interventions identifies a number of potentially useful tools which could be evaluated locally, such as that by Bramwell et al. (2020) designed to assist persons with T2DM to adjust their insulin doses and that by Daud et al. (2020) designed to assist persons with the metabolic syndrome to self-manage their health behavior.

4.7. Strengths and limitations of this scoping review

This scoping review was as comprehensive as possible in the identification of relevant papers, was rigorous in its conduct and aimed to be transparent in its reporting. This should allow replication to allow updating of the findings of this review in the future.

In line with the methods outlined by Arksey and O'Malley (2005), the papers included in this review were not formally assessed for quality. This is due to the heterogeneity of papers in terms of different designs, methodologies and focus, which makes comparison of quality difficult (Arksey and O'Malley, 2005).

5. Conclusion

This scoping review has identified the research that has been carried out to address the research priorities identified in the National Diabetes Strategy (Calleja et al., 2016). It has shown that there has not been a structured and systematic approach in addressing the priority research areas identified in this strategy. In many areas, however, there exists a body of research which can serve as a foundation stone for further studies as well as for updating clinical practice.

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Declaration of Competing Interest

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