REVIEW / SYNTHÈSE

Evidence-based risk assessment and recommendations for physical activity clearance: diabetes mellitus and related comorbidities[1]

Michael C. Riddell and Jamie Burr

Abstract: Physical activity (PA) is one of the most powerful treatment options for persons with prediabetes or diabetes. However, some elevation in risk occurs with increased PA, at least initially, and certain precautions need to be made to lower these risks, particularly if these persons are unaccustomed to exercise. We conducted a standardized search of all adverse events associated with increased PA in persons with prediabetes or diabetes (type 1 or type 2) and provided evidence-based guidelines on PA screening in these apparently high-risk individuals. A systematic literature review was performed of all studies reporting on adverse events in persons with prediabetes or diabetes. Studies included were from all designs (retrospective and prospective including randomized controlled trials) and were assessed according to evaluation criteria adapted by a consensus panel. A total of 47 studies, involving >8000 individuals, were deemed eligible. A number of these studies identified a range of mild to severe acute risks with exercise (musculoskeletal injury, hypoglycemia, foot ulceration, proliferative retinopathy, hypotension, sudden death) but the overall prevalence was low. Based on several randomized controlled trials and prospective studies in which prescribed exercise was performed at a wide range of intensities, it appears that increased PA is a relatively safe procedure with no evidence of a loss of life. Based on our assessment of the available literature, we provide a new PA risk algorithm for persons with prediabetes and diabetes and comment on the role of the patient, the qualified exercise professional, and the patient's physician in the risk screening process.

Key words: exercise, diabetes mellitus, prediabetes, adverse events, Par-Q.

Résumé : L'activité physique (PA) est un des meilleurs traitements à l'intention des personnes prédiabétiques et diabétiques. Toutefois, avec l'intensification de la pratique de l'activité physique vient une augmentation du risque, du moins au début, et il est donc indiqué de prendre des précautions pour diminuer ce risque particulièrement chez les personnes non accoutumées à l'effort physique. Nous avons réalisé une recherche systématique de tous les événements indésirables se présentant avec l'intensification de la PA chez des personnes prédiabétiques et diabétiques (type 1 et type 2) et nous présentons des directives basées sur des données probantes pour le dépistage des patients apparemment à haut risque en matière de PA. On effectue une analyse documentaire systématique de toutes les études présentant des événements indésirables s'étant manifestés chez des personnes prédiabétiques et diabétiques. Les études incluent tous les devis expérimentaux (rétrospectifs et prospectifs y compris les essais cliniques aléatoires (RCTs)); on évalue ces études en fonction des critères adaptés par consensus d'experts. Au total, 47 études comprenant plus de 8000 personnes sont retenues. Un certain nombre d'études identifient des risques associés à PA allant de faibles à graves (blessure musculosquelettique, hypoglycémie, ulcère du pied, rétinopathie proliférante, hypotension, mort subite), mais la prévalence globale est faible. À la lumière de plusieurs RCTs et études prospectives dans lesquelles on prescrit la pratique de l'activité physique à une vaste gamme d'intensités, il ressort que l'augmentation de la PA est une pratique plutôt sécuritaire non associée d'après des données probantes au décès. À partir de notre évaluation des études disponibles, nous présentons un nouvel algorithme de risque associé à la pratique de PA chez les personnes prédiabétiques et diabétiques et nous commentons le rôle du patient, du professionnel de l'exercice certifié et du médecin du patient au sujet du processus de dépistage du risque.

Mots-clés : exercice physique, diabète sucré, prédiabète, événements indésirables, Q-AAP.

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M.C. Riddell and J. Burr. School of Kinesiology and Health Science, Muscle Health Research Centre, Physical Activity and Chronic Disease Unit, York University, 4700 Keele Street, Toronto, ON M3J 1P3, Canada.

Corresponding author: Michael C. Riddell (e-mail: mriddell@yorku.ca).

[1]This paper is one of a selection of papers published in this Special Issue, entitled Evidence-based risk assessment and recommendations for physical activity clearance, and has undergone the Journal's usual peer review process.

Lay summary

Physical activity is one of the most powerful treatment options for persons with prediabetes or diabetes. Numerous health benefits occur with increased physical activity (PA), which include enhanced blood sugar and cholesterol control, the prevention of metabolic complications, and less risk of dying prematurely from cardiovascular disease. However, some elevation in risk for an adverse event occurs with increased PA, at least initially, and certain precautions need to be taken to lower these risks, particularly if these persons are unaccustomed to exercise. To help understand, and ultimately reduce, the possible risks of increased PA, we performed a comprehensive literature review of all known risks of exercise in persons with prediabetes or diabetes and, based on our findings, propose new evidence-based PA clearance guidelines for individuals diagnosed with these conditions. Overall, this comprehensive review indicates that PA is a relatively safe and feasible intervention for most persons with these identified conditions and that the risk of any serious adverse event is low. Nonetheless, certain precautions are deemed appropriate for those who have been diagnosed with diabetes and its related complications, such as cardiovascular disease, eye problems (retinopathy), nerve problems (neuropathy), and kidney problems (nephropathy). These precautions include pre-exercise clearance by a qualified exercise professional and in some cases also by a clinical specialist (i.e., a physician) familiar with these conditions and the possible threats of exercise. To assist with the decision making, we provide evidence-based risk assessment screening guidelines and decision trees for individuals with prediabetes, type 2 diabetes, and type 1 diabetes.

Introduction

Lifestyle recommendations are a first line of defense in the prevention and treatment of prediabetes and type 2 diabetes. For those already diagnosed with diabetes (either type 1 or type 2), there are considerable benefits from being physically active. In the past, several authors, professional associations, and expert consensus panels have presented guidelines and (or) recommendations for physical activity (PA) for patients with diabetes (Sigal et al. 2004, 2006, 2008; Albright et al. 2000; Constantini et al. 2005; Flood and Constance 2002; Chipkin et al. 2001; Albert and Bernbaum 1995; Draznin 2000; Physical Activity Guidelines Advisory Committee 2008; Thomas et al. 2006). While these important documents highlight the numerous benefits of PA, they generally fail to provide clear evidenced-based guidelines on risk stratification or on the absolute and relative contraindications to exercise in these seemingly high-risk individuals. What is required are clear, evidence-based recommendations on the risks and benefits of exercise and a decision tree for PA screening for use by fitness and health care professionals working with these individuals. These recommendations will help form the basis for the revised Physical Activity Readiness Questionnaire (PAR-Q) and Physical Activity Readiness Medical Examination (PARmed-X) screening process.

Definitions, etiology, and epidemiology

The term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic high blood glucose (hyperglycaemia) with disturbances of carbohydrate, fat, and protein metabolism, themselves resulting from defects in insulin secretion, insulin action, or both. Prediabetes is a term used to describe those in the population with either fasting or postglucose load glycemia higher than normal, but lower than that used for a diagnosis of diabetes. Type 1 diabetes is characterized by insulin deficiency due to destructive autoimmune based lesions of pancreatic β cells, while type 2 diabetes is caused by a combination of decreased insulin sensitivity and decreased insulin secretion. The diagnostic criteria for prediabetes and diabetes are summarized in Table 1. Table 2 shows the plasma glucose levels for diagnosis of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), both of which are commonly used to define "prediabetes". The effects of diabetes (both type 1 and type 2) include micro- and macrovascular lesions, long-term organ damage, and increased risk of premature death (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008).

The incidence and prevalence of prediabetes and diabetes in the Canadian population is thought to be high and on the increase. No accurate data on prediabetes prevalence exists in Canada, although it is estimated by the Public Health Agency of Canada that ~4 million (12.5%) people between the ages of 40 and 74 have impaired fasting glucose and ~1.8 million (5%) have impaired glucose tolerance (Public Health Agency of Canada 2008). Recent prevalence rates for type 2 diabetes in individuals ≥12 years old is estimated to be ~6% of the Canadian population (Lipscombe and Hux 2007). In persons over the age of 50 years, the prevalence of type 2 diabetes may be as high as 18% and 22% in females and males, respectively (Lipscombe and Hux 2007). Diabetes rates are particularly high in aging populations and in certain cultural communities (e.g., Asians, Southeast Asians, Caribbean, and Aboriginals). With an aging population, an increasing obesity rate, more immigration from populations who are at high risk for diabetes, and the increasing prevalence of diabetes in Aboriginal populations, diabetes prevalence is expected to increase further in the next 10–20 years. One projection estimates that the prevalence of diagnosed diabetes will increase to 2.4 million by the year 2016, with rates of about 7% across the population (Ohinmaa et al. 2004).

Diabetes is a contributing factor in the deaths of ~41 500 Canadians each year (Public Health Agency of Canada 2007), usually as a result of complications from micro- and macrovascular (small and large vessel, respectively) disease that attacks a variety of organs and tissues. Adults with diabetes are twice as likely to die prematurely as persons without diabetes, usually of cardiovascular complications. Even children with diabetes are at an elevated risk of dying from poorly managed disease (i.e., ketoacidosis or severe hypoglycaemia causing death). The risk of suffering a cardiovascular disease (CVD) related event for people with diabetes is increased 2- to 3-fold for men and 3- to 5-fold for women, compared with those without diabetes (Rydén et al. 2007). Diabetes and its complications cost the Canadian health care system an estimated $13.2 billion every year, a value that is projected to exceed $19.2 billion a year by 2020 (Ohinmaa et al. 2004).

Table 1. Diagnostic criteria for diabetes (type 1 or type 2).

(*a*) Fasting plasma glucose ≥ 7.0 mmol·L^{-1}
Fasting = no caloric intake for at least 8 h
or
(*b*) Casual plasma glucose ≥ 11.1 mmol·L^{-1} + symptoms of diabetes
Casual = anytime of the day, without regard to the interval since the last meal
or
(*c*) 2hPG in a 75-g oral glucose tolerance test ≥ 11.1 mmol·L^{-1}

Note: A confirmatory laboratory test (*a*, *b*, or *c*) must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. In individuals in whom type 1 is suspected, treatment should be initiated to avoid rapid deterioration. Adapted with permission from the Canadian Diabetes Association (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008).

Table 2. Plasma glucose levels for the diagnosis of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (i.e., prediabetes).

Glucometabolic category	FPG (mmol·L^{-1})		2hPG in the 75-g OGTT (mmol·L^{-1})
Normal	<5.6		<7.8
At risk	5.6–6.0		<7.8
IFG (prediabetes)	6.1–6.9		NA
Isolated IFG (prediabetes)	6.1 6.9	and	<7.8
Isolated IGT (prediabetes)	<6.1	and	7.8–11
IFG and IGT (prediabetes)	6.1 6.9	and	7.8–11
Diabetes mellitus	≥7.0	or	≥11.1

Note: There is no worldwide consensus on the definition of IFG. The Canadian Diabetes Association continues to define IFG as an FPG value of 6.1 to 6.9 mmol·L^{-1} while the American Diabetes Association recommend that IFG is defined as a FPG value between 5.6 and 7.0 mmol·L^{-1}. FPG, fasting plasma glucose; OGTT, oral glucose tolerance test. Adapted with permission from the Canadian Diabetes Association (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008).

Measuring diabetes-related metabolic control and its relationship to micro- and macrovascular complications

Glycated hemoglobin (HbA1c), is an integrated summary of circadian blood glucose levels during the preceding 2–3 weeks, and is a blood measurement used to assess metabolic control in persons with diabetes. Although not currently used as a screening tool in Canada, individuals with a HbA1c of ≤6.0% are considered normal, while values of 6.1%–6.9% could be considered as having prediabetes and those with values ≥7.0% are considered as having diabetes (Buell et al. 2007). However, these cut points for diagnosis of prediabetes and diabetes may not be appropriate for certain high-risk ethnicities (Mohan et al. 2010). The HbA1c measurement is the current standard for the measurement of metabolic control in persons already diagnosed with diabetes. The recommended HbA1c target for persons with diabetes is an HbA1c of ≤7.0% (with normal being 4.0%–6.0%) (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2008), based on epidemiologic analysis showing that levels >7.0% are associated with a significant increase in the risk for developing both micro- and macrovascular complications, regardless of the type of diabetes or the underlying treatment (Stratton et al. 2000; Standl et al. 1996; Keen 1994). This level of control is often difficult to achieve in patients with type 1 diabetes, as aggressive insulin treatment poses increased risk for hypoglycemia, coma, and even death. For persons with type 2 diabetes, a normal HbA1c is also challenging but is achievable with intensification of antidiabetic therapy and lifestyle intervention (Vinik 2007).

An evaluation of a patient's HbA1c prior to any intervention (i.e., lifestyle or pharmacological) is helpful to determine the effectiveness of treatment and the risk of the patient developing any complication from hyperglycemia including CVD. The relationship between HbA1c and CVD is considered to be a continuum, such that with each 1% increase of HbA1c above normal (e.g., 5.5% to 6.5%) there is a defined increased risk for an adverse cardiovascular event (Stratton et al. 2000). Thus, the HbA1c measurement should be considered useful as part of the assessment of future risk of CVD and other diabetes-related complications in people with diabetes.

The link between diabetes and CVD

The association between dysglycemia and CVD event risk is strong (Gerstein 1997). Because of this close relationship, the term "cardiometabolic" disease is sometimes used to describe a cluster of abnormalities in both the metabolic and cardiovascular systems that predispose an individual to developing heart disease and or stroke (Després 2008). Unfortunately, a patient with diabetes (either type 1 or type 2) may present with an acute major cardiac event even though the individual was previously asymptomatic for coronary artery disease (CAD) (Alexander et al. 2000). Those with diabetes who also have elevations in waist circumference, increased triglycerides, hypertension, advanced age, a history of smoking, and a family history of CVD have the highest risk for CVD-related events. A CVD event risk assessment can be calculated for persons with type 2 diabetes from the United Kingdom Prospective Diabetes Study (UKPDS) risk engine to assist health care providers in determining risks for future cardiovascular events (Stevens et al. 2001).

Large scale epidemiological studies show that persons with diabetes (either type 1 or 2) frequently have hypertension, dyslipidemia, coronary artery disease, and (or) myocardial diastolic dysfunction, even at the time of diabetes diagnosis (Schannwell et al. 2002; Raev 1994; Karamitsos et al. 2007). It is also well established that individuals with both type 1 and type 2 diabetes have at least twice the mortality and morbidity related to myocardial infarction (MI) as the general public (Marwick et al. 2002). The incidence of CAD and atypical CAD-associated symptoms is higher in the diabetic population than in the nondiabetic population (Ledru et al. 2001; Nesto 2001; Scheidt-Nave et al. 1990). Some estimate that 5%–10% of middle-aged or older individuals with diabetes who do not have classic symptoms of ischemia have clinically significant CAD (Koistinen 1990; Langer et al. 1991), and these asymptomatic individuals are at elevated risk for having an acute cardiovascular event (Bax et al. 2007). Once a person with diabetes has suffered a cardiac event, the prognosis is often worse than those who do not have a metabolic condition. For example, following an initial MI, persons with diabetes are nearly twice as likely to die from sudden cardiac death comparedwith nondiabetic individuals (Miettinen et al. 1998). Thus, middle-aged and older individuals with diabetes

should be considered at high risk for future cardiovascular events, even if they are not yet diagnosed with CVD, particularly if they are under poor glycemic control. Some epidemiological evidence exists that vigorous exercise itself is a major trigger of MI in persons with diabetes (Mittleman et al. 1993), particularly in those who are normally sedentary. As a result, exercise has long been thought to place these individuals with diabetes at a high risk for an adverse event during exercise, at least transiently. This high risk often persuades clinical investigators and professional organizations to recommend vigilant CVD screening before starting a PA program that is more vigorous than walking.

Evidence-based benefits and risks of PA in individuals with metabolic disease

PA is a powerful intervention for metabolic disease prevention and treatment. Moreover, regular PA lowers metabolic disease risk and significantly attenuates type 2 diabetes development (Tuomilehto et al. 2001; Knowler et al. 2002; Kosaka et al. 2005; Pan et al. 1997). It is also well known that being more physically active confers a lower long-term risk of having a cardiac event or of dying prematurely among people with prediabetes or diabetes (Church et al. 2005; Hu et al. 2005, Gregg et al. 2003). An extensive review of the beneficial effects of PA in persons with a metabolic disease can be found in a recent report by the Physical Activity Guidelines Advisory Committee published by the United States Department of Health and Human Services (Physical Activity Guidelines Advisory Committee 2008). While several authors have commented previously on the CVD event risks associated with exercise in diabetes (Constantini et al. 2005; Flood and Constance 2002; Chipkin et al. 2001; Albert and Bernbaum 1995; Draznin 2000; Gaudet-Savard et al. 2007; Graham and Lasko-McCarthey 1990; Bernbaum et al. 1989; Kanade et al. 2006), no attempt has been made to systematically document the adverse events in persons with metabolic disease. As such, several questions remain with respect to PA and metabolic disease: (*i*) what are the risks associated with increased PA for each type of metabolic disease–condition; (*ii*) what are the absolute and relative contraindications of exercise that should be considered in screening individuals with a metabolic condition; and (*iii*) who is qualified to screen and prescribe such an exercise program?

In the following sections we highlight the documented risks of exercise for persons with a metabolic disease (i.e., metabolic syndrome, prediabetes, diabetes) and use a standardized search strategy (Appendix A) to provide evidence of adverse events associated with increased PA. Based on this evidence, we provide recommendations about exercise screening, contraindications to exercise, and the role of the qualified exercise professional (QEP) in evaluating and prescribing exercise for persons with a metabolic condition–disease.

The following section was written by the consensus panel that guided the overall revision of the PA clearance process. This information is reprinted in each of the systematic review papers so that these reviews can stand alone from the paper describing the overall consensus process (Jamnik et al. 2011):

PA participation is recommended and beneficial for all asymptomatic persons and for persons with chronic diseases (Warburton et al. 2006, 2007). However, the PA participation of persons with certain chronic disease conditions or constraints may need to be restricted. The Physical Activity Readiness Questionnaire (PAR-Q) is a screening tool completed by persons who plan to undergo a fitness assessment or to become much more physically active; for example, when initiating PA participation that is beyond a person's habitual daily activity level or when beginning a structured physical activity or exercise program. Screening is also recommended when a person is joining a health club, commencing a training program with a fitness professional or joining a sports team. If a person provides a positive response to any question on the PAR-Q, he or she is directed to consult with his/her physician for clearance to engage in either unrestricted or restricted physical activity.

The Physical Activity Readiness Medical Evaluation (PARmed-X) is a screening tool developed for use by physicians to assist them in addressing medical concerns regarding PA participation that were identified by the PAR-Q. Recent feedback from physical activity participants, fitness professionals and physicians has brought to light substantial limitations to the utility and effectiveness of PAR-Q and PARmed-X screening. In short, the exercise clearance process is not working as intended and at times is a barrier to PA participation for those persons who may be most in need of increased physical activity. The aim of the present project is for experts in each chronic disease, together with an expert panel, to revise and increase the effectiveness of the PAR-Q and PARmed-X screening process using an evidence-based consensus approach that adheres to the established Appraisal of Guidelines for Research and Evaluation (AGREE). An important objective of this project is to provide evidence-based support for the direct role of university-educated and QEP in the exercise clearance process. An example of a QEP is the Canadian Society for Exercise Physiology Certified Exercise Physiologist (CSEP-CEP) or an American College of Sports Medicine (ACSM) Clinical Exercise Specialist.

The AGREE process was developed by a group of researchers from 13 countries to provide a systematic framework for assessing the quality and impact on medical care of clinical practice guidelines (CPGs) (AGREE Collaboration 2001, 2003). The AGREE Collaboration published the rigorous development process and associated reliability and validity data of the AGREE instrument based on a large-scale study focusing primarily on CPGs (AGREE Collaboration 2001). The AGREE instrument is now a commonly used tool for assessing CPGs and other health management guidelines (Lau Obesity Canada Clinical Practice Guidelines Steering Committee and Expert Panel 2007). The instrument is made up of 23 distinct criteria distributed across 6 subscales termed "domains". The AGREE criteria were customized for use in the present project to assess the formulation of risk stratification and PA participation recommendations for each of the critical chronic diseases. In addition to adhering to the AGREE process, the Level of Evidence (1 = randomized control trials (RCTs); 2 = RCTs with limitations or observational trials with overwhelming evidence; 3 = observational studies; 4 = anecdotal evidence) supporting each PA screening recommendation and the Grade (A = strong; B = intermediate; C = weak) of the PA screening recommendation were assigned by applying the standardized Level and Grade

of Evidence detailed in the consensus document (Warburton et al. 2011).

The overall purpose of this paper is to provide an evidence-based risk assessment of PA participation in persons with prediabetes, type 2 diabetes, and type 1 diabetes. Evidence-based recommendations about the absolute and relative contraindications to PA are also provided along with a proposed decision tree that can be used for PA screening purposes. Finally, the role of the patient, the QEPs, such as the CSEP-CEP, and the patient's physician in the screening process is also discussed. For this, a comprehensive and critical evaluation of the relevant literature was conducted, along with an assessment of the risk/benefit ratio of exercise for the management and (or) prevention of these metabolic diseases. The strength of evidence for or against exercise of differing forms and intensities was weighted according to the AGREE Instrument and the associated levels and grade of evidence.

Methods

In consultation with the consensus panel and a university librarian, we developed a comprehensive search strategy and performed a computer-assisted query of the following electronic databases: Medline, CINAHL, SPORTdiscus, EMBASE, Cochrane Database of Systematic Reviews (DSR), American College of Physicians (ACP) Journal Club, and Database of Abstracts of Reviews of Effects (DARE). We sought English language articles indexed before the second week of February 2008 and searched both keywords and Medical Subject Headings (MeSH) to keep the search intentionally broad. Keywords included diabetes, metabolic disorders, risk, adverse event, exercise, and PA. The complete metabolic search strategy is provided in Appendix A. For the purpose of this review, we limited the metabolic disorders to metabolic syndrome, prediabetes and diabetes. Many of these studies included patients in whom obesity also was prevalent. This main search was supplemented with articles identified from the reference lists of retrieved articles as well as by our knowledge of articles that were not captured by the computer-based search.

One author (J.B.) reviewed titles and abstracts of the identified articles, removed duplicates, and retrieved all potentially relevant literature. Studies conducting a PA training intervention and (or) exercise testing in which adverse events were reported among persons diagnosed with metabolic syndrome, prediabetes, or diabetes were deemed eligible. A second author (M.C.R.) further reviewed the same list to ensure agreement on article relevance and significance. Specific attention was given to articles examining the risks of PA participation as well as reports of adverse events. To be as inclusive as possible, any adverse event reported (expected or unexpected) were tabulated even if they were not deemed to be directly attributed to any PA intervention.

Results

Our initial search identified a total of 4197 prospective citations based on key words (Table 3). After initial screening, 355 were deemed potentially eligible, while the other studies were excluded on the basis of their title or abstract because they were deemed not relevant to the question under study. Main reasons for exclusion were PA intervention was not included or PA participation was not monitored, subjects did not have prediabetes or diabetes, and mention of adverse events was not made or the term "risk" was not used in the context of adverse events. On secondary screening, 47 met the inclusion criteria (i.e., had at least some mention of adverse events or stated that adverse events did not occur, and the risks for persons with a metabolic disease were identifiable from those observed in controls). Of these, 35 articles had quantifiable adverse event rates per exercise hour. Twenty-two of these articles definitively stated that there were "no adverse events" related or attributed to exercise, while 13 implied that no adverse events occurred (i.e., gave dropout information that did not appear to be related to an adverse event, such as lack of time or that the subject moved, etc.). Ten articles gave specific information on adverse events associated with the intervention. A detailed tabulation of all relevant articles is shown in Table 4.

Study characteristics

A total of 47 studies were included, involving greater than 6500 subjects. In general, a majority of the studies were conducted on middle-aged men and women (Table 3). Approximately 45% of the studies were RCTs, ~25% were prospective-intervention trials or prospective nonintervention trials, ~20% were cross-sectional in nature, and ~10% were retrospective. A majority of studies had supervised exercise training paradigms and approximately half of the exercise training programs were deemed to be at moderate to vigorous intensity or included a graded exercise test. In the RCT studies, the PA intensities varied from walking to vigorous exercise for a brief duration.

Adverse events documented

In all identified studies, no clear definition for the term "adverse event" was found. In the few articles that did document adverse events ($n = 12$ studies), authors documented several parameters that they individually felt were adverse events from musculoskeletal soreness to more serious clinical complications. The total number of adverse events could not be calculated, as several studies failed to report actual event numbers or because the events in the subjects with the metabolic condition were not reported separately from the controls. Acute exercise testing (maximal or submaximal) was frequently associated with potentially deleterious events, including excessive hypertension (systolic blood pressure >260 mm Hg; diastolic blood pressure >115 mm Hg), exercise hypotension (a drop in systolic blood pressure below standing resting blood pressure), and electrocardiogram (ECG) changes indicating poor perfusion and angina, but there were no reports of loss of life. There was no documented loss of life in any of the prospective studies that appeared temporally related to PA participation.

In most studies, it was not possible to determine if the adverse events were temporally linked to PA. Two studies (Bernbaum et al. 1989, Faglia et al. 2002) reported adverse events during exercise testing in persons with diabetes, 1 study reported adverse events immediately after testing in prediabetics (Schneider et al. 1984), while the remaining reported adverse events during training–PA intervention. The majority of events were cardiovacular-related in the studies

Table 3. Metabolic search summary.

Total titles searched	4197
Total articles retrieved for analysis (including hand searched)	355
Studies with reference to adverse events (not reviews)	47
Studies that definitively stated adverse events associated with PA	12
Studies that did not explicitly state a lack of adverse events with PA, but the lack of events was implicit based on information about dropouts	13
Studies specifically stating no adverse events occurred with PA	22
Studies with quantifiable event rate per exercise hours	35
Retrieved article with relevance to risk: breakdown by study design	
Cross-sectional studies (Level 3)	9
Retrospective studies (Level 3)	4
Prospective intervention studies (Level 2)	11
Prospective noninterventional studies (Level 3)	2
RCTs*	21
Total	47
Exercise mode (excludes reviews)	
Cycle	7
Walk–jog	6
Mixed aerobic	11
Resistance	9
Mixed aerobic and resistance	12
Cardiac–diabetes rehabilitation	2
Intensity percentage of articles (highest intensity used if spans more than 1 category)	
Light	0
Light– moderate	4.3
Moderate	32.6
Moderate–vigorous	32.6
Vigorous	15.2
Very hard	8.7
Maximal	6.5
Adverse article breakdown by gender, %	
Male only	20.4
Female only	12.2
Both male and female	67.3
Ages (percentage of decade representation)	
10	1.4
20	2.7
30	12.3
40	19.2
50	35.6
60	21.9
70	5.5
80	1.4

Note: PA, physical activity, RCT, randomized controlled trial.

*Note that adverse events were not standardized outcome measures and patients were screened with a graded exercise test prior to study intervention) (Level 2 or Level 3).

reporting on exercise testing. In most studies, it was not possible to estimate an adverse event rate as the exercise frequency, session duration, or intervention duration was not reported. In other studies, the actual event number was not mentioned but rather the percentage of subjects that reported having adverse events was given. In a number of studies (n = 22), the authors only briefly stated that "no adverse events occurred" or "were found". The most common adverse events reported during exercise testing or training were musculoskeletal soreness–injury, hypotensive or hypertensive response, hypoglycemia, or an "exacerbation of a medical problem". Reports of retinal hemorrhage and foot ulceration also occurred but were rare (Schneider et al. 1992). Only 1 case of worsening angina was cited in a recent RCT of people with type 2 diabetes (Sigal et al. 2007). Overall, cardiovascular symptoms were rare during PA intervention studies. One epidemiological study from Germany (Unverdorben et al. 2007), examining risk predictors and frequency of cardiovascular symptoms during cardiac rehabilitation programs, found high levels of mild to moderate cardiovascular symptoms in a mix of diabetic and nondiabetic patients (828 symptoms were reported by 538 patients in ~674 000 patient exercise hours). However, in that study, previous MI and diabetes had no statistically significant impact on cardiovascular

Table 4. Details of the studies included from the standardized search strategy.

Prediabetes					
Reference	Subjects	Prescreened	Supervised exercise	No. of subjects exercised	Study type
Pan et al. 1997	577 classified as having IGT	Yes	No	Exercise 57, diet + exercise 46	Retrospective
Irwin et al. 2003	173 sedentary, overweight prediabetic post-menopausal women aged 50 to 75 y	Yes	No	87	RCT
Knowler et al. 2002	3234 nondiabetics with elevated fasting and post-load glucose	Yes	Guidance not supervision	1082 placebo, 1073 metformin drug	RCT
Ueno et al. 1997	25 obese with fatty liver	Yes	No	15	RCT
Type 2 DM					
Agurs-Collins et al. 1997	64	Yes	Yes	32	RCT
Baldi and Snowling 2003	18 type 2 DM, obese	Yes	Yes	18	RCT
Balducci et al. 2004	120 type 2 DM	Yes	Yes	62	Prospective intervention
Brandon et al. 2003	Community dwelling adults with type 2 DM (66.1 y average)	Yes	Yes	29	RCT
Gaudet-Savard et al. 2007	43 type 2 DM men, 1555 exercise sessions	Yes	Yes	43	Cross-sectional
Castaneda et al. 2002	62 community dwelling Latino>55 and type 2 DM of at least 3 y (31 usual care and residence. Training, 31 control usual care)	Yes	Yes	31	RCT
Cauza et al. 2006	Type 2 DM patients, 22 men and 22 women, split equally into ST and ET groups	Yes	Yes	22 Endurance, 22 resistance	Prospective intervention
Dunstan et al. 1997	55	Yes	Yes	Moderate exercise 25, light exercise 24	RCT
Dunstan et al. 1998	15 formal circuit exercise,12 control	Yes	Yes	15	RCT
Dunstan et al. 2002	36 sedentary, overwieght type 2 DM men and women	Yes	Yes	16	RCT
Giannopoulou et al. 2005	33 postmenopausal, obese (>30) women	Yes	Yes	22	Prospective intervention
Honkola et al. 1997	38 type 2 DM, 18 exercise, 20 control	Not stated	Yes	18	RCT
Ibañez et al. 2005	10 untrained, sedentary men, newly diagnosed type 2 DM, highly screened	Yes	Yes	10	Prospective interventional
Inoguchi et al. 2000	140 asymptomatic (ischemia) type 2 DM	Yes	Yes	140	Cross-sectional
Loimaala et al. 2003	49 male, type 2 DM (53.3s±5.1 y)	Yes	1 endurance session per week supervised	25	RCT
Loimaala et al. 2007	Type 2 DM	Yes	Partial supervision	24	RCT
Maiorana et al. 2002	16, type 2 DM (52 ±2 y) ,14 male, 2 female	Yes	Yes	16	RCT
Mourier et al. 1997	24 mildly obese, type 2 DM (45±2 y), 20 male, 4 female	Yes	Yes	12	RCT
Ozdirenç et al. 2004	Type 2 DM (hospitalized) patients. 23 in exercise group, 21 in control	Yes	Yes	23	RCT
Praet et al. 2008	11 type 2 DM male patients BMI>30	Yes	Yes	11	Prospective interventional
Schneider et al. 1984	20 Sedentary, mildly obese (within 20% of ideal body weight), type 2 DM (11 controls)	Yes	Yes	20	Prospective interventional
Sigal et al. 2007	251 type 2 DM (39–70 y)	Yes	Supervision for first 4 wk, biweekly thereafter	Aerobic 60esistance 64, combined 64	RCT
Tokmakidis et al. 2004	Screened (for CHD, etc) sedentary type 2 DM women	Yes	Yes	9	Prospective interventional
Tudor-Locke et al. 2004	Type 2 overweight–obese, sedentary	Yes	No	24	RCT
Type 1 and type 2 DM (or undefined diabetes)					
Balducci et al. 2006	Type 1 and 2 DM patients. 31 exercise, 47 control	Yes	Yes	31	RCT
Bernbaum et al. 1989	29 patients with DM and diagnosis of visual impairment	Yes	Yes	29 (20 IDDM, 9 NIDDM)	Prospective noninterventional
Konstantinidou et al. 2002	48 patients with DM	Yes	Partial supervision	36	RCT

Mode	Intensity	Adverse events mentioned	Events per exercise hours in patient group
Mixed aerobic	**Moderate–strenuous** (perceived based on examples of activity)	11 died during the course of the study: no deaths in exercise only group, 3 deaths in diet group (2 cancer, 1 septicemia), 5 in the diet + exercise (1 stroke, 2 cancer, 1 accidental, 1 Crohn's). 3 deaths in control (1 pneumonia, 2 cirrhosis)	No records of actual events during activities
Mixed aerobic exercise	GXT **maximal** 40%–75% HR_{max} **vigorous**	No treadmill tests were terminated for reasons other than volitional fatigue. No injuries were reported as a result of the exercise intervention	0 per 14 355 h 0 GXT
Mixed aerobic	**Moderate**	The rate of gastrointestinal symptoms was highest in the metformin group, and the rate of musculoskeletal symptoms was highest in the lifestyle–intervention group (Table 3). Hospitalization and mortality rates were unrelated to treatment. No deaths were attributed to the study intervention	—
Mixed aerobic	**Moderate–vigorous**	No complications	—
Mixed aerobic	**Moderate**	Reasons for not completing the study included medical problems not directly related to having diabetes or to program participation	0 per 1008 h
Resistance	**Moderate–vigerous**	No complaints or injuries (except for some expected muscle soreness in early stages)	Not quantifiable
Mixed aerobic and resistance	**Moderate–vigorous**	Throughout the study, no adverse effects occurred in any patient	0 per 8705 h
Resistance	50%–70% 1RM **moderate**	Very high drop-out rate in both control (35%) and Exc (45%) groups. Reasons for drop out: lack of time, disease got worse (does not say if this is linked to the exercise), spouse became ill, or they relocated to another city	Not quantifiable
Cycle	60% $\dot{V}O_{2\ max}$ **moderate**	**No adverse events reported**. Conclusion: safe for middle-aged men with NIDDM to exercise in the fasted state	0 per 1555 h
Resistance	**Moderate–hard**	2 were lost to medical reasons not related to the study	0 per 1116 h
1. Resistance 2. Aerobic	1. **Moderate** 2. 60% $\dot{V}O_{2\ max}$	One subject did not complete the testing due to health reason unrelated to research.	0 per 396 h
Cycle	GXT **maximal** and exercise **light–moderate**	6 subjects withdrew because of changes in medication or other time commitments. No mention of adverse	0 per 776
Resistance	50%–55% 1RM **moderate**	Of the subjects who commenced the training program, 1 nonrelated surgery, 1 change in medication, 2 time issues	0 per 630 h
Resistance	50%–85% 1RM **hard–very hard**	Other than transient musculoskeletal soreness, no major problems or injuries were reported from either the RT and WL or the WL group	0 per 864 h
Walk	**Hard–vigorous**	3 women dropped out due to compliance problems, 4 women dropped out with health problems unrelated to the study	0 per 767 h
Resistance (circuit)	**Moderate**	The exercise training program was safely done by all subjects	0 per 360 h
Resistance	**Hard–vigorous**	9 completed the study successfully, 1 was excluded for noncompliance	0 per 300 h
Walk	GXT (Bruce protocol) **maximal**	38.6% had impaired performance on exercise test from noncardiac limitations. No serious cardiovascular side effects were observed	0 GXT
Mixed aerobic and resistance	65%–75% $\dot{V}O_{2\ max}$ 70%–80% 1RM **hard**	1 subject from the exercise group withdrew from the study because of lack of time for training	0 per 2400 h
Mixed aerobic and resistance	**Vigorous**	"None of the patients had a history or clinical evidence of micro vascular complications or coronary artery disease on treadmill exercise stress test."	0 per 3060
Mixed aerobic and resistance	**Moderate–vigorous**	All completed 24 exercise sessions and the exercise regimen was well tolerated with no adverse events. No significant adverse events occurred during exercise testing procedures or the training sessions	0 per 1176 h
Cycle	75%–85% $\dot{V}O_{2\ max}$ **hard**	Compliance and tolerance was good. No subject dropped out for medical reasons	0 per 192 h
Mixed aerobic and resistance	**Hard**	There was no metabolic or other complications related to the exercise musculoskeletal or cardiovascular program	0 per 92 h
Mixed aerobic and resistance	50%–60% 1RM or 50%–60% max watts (cycle) **moderate**	Minor hypoglycemia in some subjects. 1 overload injury in knee. No major complications reported	1 per 248 h
Mixed aerobic	50%–75% $\dot{V}O_{2\ max}$ **moderate–vigorous**	2 patients with symptomatic hypotension followed max exercise (transient) while untrained. 6 patients had asymptomatic postexercise hypotension. No subjects experienced clinically relevant visual, renal, or neurological deterioration	2 per 270 h minor, 0 per 270 serious
Mixed aerobic	60%–75% HR_{max} **hard**, resistance = **moderate hard**	4 serious adverse events (hospitalization), 1 each of elective hysterectomy, elective hernia repair, spinal stenosis, **worsening angina.** Other minor musculoskeletal events were reported	1 per 3, 72 h
Resistance	60% 1RM **moderate**	The exercise regimen was well tolerated; no orthopedic injuries or cardiovascular complications occurred during the exercise sessions	0 per 288 h
Walk	**Light–moderate**	No "noteworthy" musculoskeletal pain or problems during the intervention	Not quantifiable
Walk	50%–85% HRR **very hard effort**	"No adverse effects throughout the entire study were observed."	0 per 25 792
Cycle	GXT **maximal**	Test terminated due to elevated blood pressure in 6, fatigue in 20, dyspnea in 1, hypotension and dizziness in 1. Hypertension = systolic blood pressure greater than 30 mm Hg over baseline or if systolic exceeded 240 mm Hg for individuals with complete vision loss	2 GXT (8 with hypertension cutoff)
Mixed aerobic and resistance	50%–70% HR_{max}, **moderate** resistance, **moderate–vigorous**	"There were no musculoskeletal, cardiovascular or other complications related to the exercise programs."	0 per 2592 h

Table 4 (*concluded*).

Prediabetes					
Reference	Subjects	Prescreened	Supervised exercise	No. of subjects exercised	Study type
Banzer et al. 2004	952 (250 DM, 702 no diabetes)	Yes, medical history and physical evaluation	Yes	250	Prospective intervention
Lemaster et al. 2003	391 diabetic with a prior history of foot ulcer	Yes	NA	391	Prospective noninterventional
Oh-Park et al. 2002	22 diabetic patients undergoing hemodialysis for end-stage renal disease	Yes	Yes	22	Prospectiventervational
Schneider et al. 1992	255 = 200 type 2 DM, 55 type 1 DM	Yes	Yes	255	Retrospective
Kouidi et al. 2004	48 hemodialysis patients (25–67 y)	Yes	Yes	48	Prospective intervention
Unverdorben et al. 2007	1935 cardiac rehabilitation patients ≈ 674 000 patient-hours, 828 symptoms in 528 patients	NA	NA	—	Retrospective
Moore et al. 1998	8 patients on hemodialysis, 6 male, 2 female	Yes	Yes	8	Crosssectional
Mittleman et al. 1993	1228 interviewees (232 with DM)	No	No	4.4% or 520 who reported moderate–vigerous activity≥6.0 METs in the hour before MI	Case-crossover
Kanade et al. 2006	23 control, 23 with unilateral current plantar ulceration, 16 healed unilateral PFA, 22 healed unilateral TTA	Yes	Yes	61	Cross-sectional
Type 1 DM					
Fuchsjäger-Mayrl et al. 2002	All type 1 DM 18 subjects in exercise group, 8 in control	Yes	Yes	18	Cross-sectional
Lehmann et al. 1997	20 (13 male, 7 female) type 1 DM	Yes	No	20	Prospective intervention
Matteucci et al. 2006	35 type 1 DM, 74 first degree relatives, 95 controls	Yes	Yes	35	Cross-sectional
Mosher et al. 1998	10 type 1 DM, 10 control, male adolescents	Yes	Yes	10	Prospective intervention
Cruickshanks et al. 1992	818 type 1 DM, <30	No	No	—	Cross-sectional
Cruickshanks et al. 1995	606 type1 DM, <30	No	No	—	Cross-sectional
Other relevant articles					
LaPorte et al. 1986	696 type I DM	NA	NA	696	Prospective noninterventional
Siscovick et al. 1984	Male primary cardiac arrest patients (133)	NA	NA	133	Retrospective
Tanasescu et al. 2003	Health Professionals Follow up Study n = 51 529, Diabetics = 3058	NA	NA	3058	Retrospective
Van Camp and Peterson 1986	51 303 patients exercised 2 351 916 h	NA	NA	51 303 (2 351 916 h)	Retrospective
Colbert et al. 2000	(n = 5327) Injuries = 698 men, 169 women	NA	NA	5327	Cross-sectional
Hu et al. 2001	5125 female diabetic nurses	NA	NA	5125	Prospective noninterventional

Note: 1RM, one-repetition maximum; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DM, glucose tolerance; MI, mitochondrial infarction; NA, not applicable; NIDDM, non-insulin-dependent diabetes mellitus; PA, physical activity; PFA, partial foot sumption; $\dot{V}O_{2\,peak}$, peak oxygen consumption.

Mode	Intensity	Adverse events mentioned	Events per exercise hours in patient group
Mixed aerobic	45%–85% HHR **moderate–vigorous**	Diabetic patients withdrew more often because of an exacerbation of a medical problem, although cardiac conditions precluded program completion at a similar rate in both groups (9.8% vs. 8.5% of nondiabetics)	9.8% vs. 8.5% in diabetics vs. controls
Walk	—	Risk of foot ulcer increased with acute changes in exercise. Participants who were active in the long term were at 50% less risk compared with those least active. Effect of activity on foot ulcer risk was not dependent on presence of sensate or insensate feet	Not quantifiable
Mixed aerobic and resistance	GXT (cycle) **moderate**, resistance training **moderate**	18 out of 22 patients completed all training. 3 could not complete because medical problems unrelated to exercise, such as sepsis, back injury, and diabetic foot complications. 1 patient excluded due to knee pain during cycling, which resolved soon after stopping cycling. **No patient developed major complications from the program**	0 GXT, 0 per 341 h
Mixed aerobic	50%–75% HRR **hard**	12% had exercise-related injuries to preclude exercise for at least 1 wk. 10% of those with retinopathy developed retinal hemorrhage (all within first 3 mo) Minor foot lesions common. No SCD, only 1 new onset of angina	Non-major 31 per 3060 h, major 26 per 3060 h, all 57 per 3060 h
Mixed aerobic and resistance	60%–80% HR_{max}, **moderate** resistance GXT (Bruce protocol) **moderate–vigorous**	No adverse events	0 per 17 856 0 GXT
Rehabilitation	—	DM had no significant (statistically) impact on cardiovascular symptoms. Those who did report events revealed overexertion, heart failure, and hypertension as predictive risk factors of cardiovascular symptoms	Total symptoms 828 out of 674 000
Cycle	GXT **maximal** and 60% $\dot{V}O_{2\ peak}$ during training, **moderate**	Orthostatic hypotension reported. Resulting from fluid lost from dialysis, as well as an inappropriate decrease in vasoconstriction and heart rate. Only becomes a problem after prolonged exercise with dialysis	0 GXT
NA	NA	RR of M.I. in the hour after heavy PA, as compared with less strenuous PA or none, was 5.9 (95% CI, 4.6 to 7.7). RR of MI in the hours after heavy PA, as compared with less strenuous PA or none was 18.9 (95% CI 7.4–47.7). Among people who usually exercised less than 1, 1 to 2, 3 to 4, or 5 or more times per wk, the respective RR were 107 (95% CI, 67 to 171), 19.4 (9.9 to 38.1), 8.6 (3.6 to 20.5), and 2.4 (1.5 to 3.7)	NA
Walk	—	Walking capacity and performance decrease with progression of foot complications. Diabetic foot is at increased risk for plantar injury, risk progresses with injury. Alternative forms of nonweight bearing activity should also be included	
Cycle	60%–70% Karvonen **vigorous**	3 patients discontinued due to time constraints, 2 patients dropped out of follow-up training due to personal reasons (no specific mention of adverse events)	0 per 576
Mixed aerobic	50%–70% $\dot{V}O_{2\ max}$ **moderate–vigorous**	Mild hypoglycemic episodes occurred in all patients at some point. Overall frequency of severe hypoglycemic episodes reduced pre–post (0.14 to 0.10 per patient year). No major (hospitalization) events	0 per 880 h
Cycle	GXT **maximal**	No patient presented with exercise-induced angina. *Nondiabetic controls showed that SBP response was associated with HB A1c levels*	0 GXT
Mixed aerobic and resistance	GXT **maximal** Training **moderate–vigorous**	All subjects completed the 12 weeks of training without injury or illness. 1 hypoglycemia after training	0 per270 h
—	—	Decreased risk of retinopathy in those more physically active	
—	—	No relationship between PA at any intensity and retinopathy	
Mixed aerobic and resistance	—	Negative association between PA and CVD and overall mortality. Those who participated in team sports were less likely to report macrovascular disease (only males — but data began in 1950 when females were less involved in sport). Activity early in life may not be associated with adverse health effect and may be beneficial	
Mixed aerobic and resistance		Did not specifically consider metabolic variables in risk (other than obesity). "Efforts to discourage clinically healthy persons at risk of PCA from continuing to engage in vigorous exercise may be inappropriate."	
Mixed aerobic	**Moderate**	Total PA is associated with a reduced risk of CVD, CVD death, and total mortality in type II DM. Walking and walking pace (independent of walking hours) are inversely associated with CVD, CVD death and total mortality	
Rehabilitation	**Moderate**	The incidence rates per million patient hours of exercise were 8.9 for cardiac arrests (1 per 111 996 patient-hours), 3.4 for myocardial infarctions (1 per 293 990 patient-hours), and 1.3 for fatalities (1 per 783 972 patient-hours).	
Self-reported walking or running. Referent cases of injury in general population	—	Significant. Lower risk of walking vs. running in young (<45 y) $R = 0.75$ men, nonsignificant in women (but still decreased). No effect of greater amounts of walking. Higher risk in runners doing 15–30 or 30+ min·day^{-1} vs. <15 min in men. Conclusion: walking can safely be recommended	867 total injuries
Mixed aerobic and resistance	**Moderate to vigorous**	Levels of PA were inversely associated with coronary heart disease and ischemic stroke. Faster usual walking pace was independently associated with lower risk. Therefore, in the long term PA has a beneficial effect on CVD events	Those with greater amounts of weekly PA have a lower risk of total cardiovascular events (includes both exercise and nonexercise time)

diabetes mellitus; ET, endurance training; GXT, graded exercise test; HR_{max}, maximal heart rate; IDDM, insulin-dependent diabetes mellitus; IGT, impaired amputation; RCT, randomized control trial; RR, relative risk; SBP, systolic blood pressure; TTA, trans-tibial amputations; $\dot{V}O_{2\ max}$, maximal oxygen con-

symptoms, whereas perceived overexertion, a low exercise capacity, and chronic heart failure all increased the relative risk for symptoms (Unverdorben et al. 2007).

In virtually all prospective studies, participants underwent some form of pre PA screening to eliminate high-risk CVD patients. Many of the studies had full or partial exercise supervision. In only 6 of 47 studies (~13%) were the exercise sessions unsupervised.

Of the 47 studies reporting on adverse events or lack thereof, 22 (Knowler et al. 2002; Gaudet-Savard et al. 2007; Avery et al. 1997; Baldi and Snowling 2003; Balducci et al. 2004, 2006; Honkola et al. 1997; Inoguchi et al. 2000; Irwin et al. 2003; Konstantinidou et al. 2002; Kouidi et al. 2004; Lehmann et al. 1997; Loimaala et al. 2007; Maiorana et al. 2002; Mosher et al. 1998; Mourier et al. 1997; Oh-Park et al. 2002; Ozdirenç et al. 2004; Tokmakidis et al. 2004; Tudor-Locke et al. 2004; Dunstan et al. 2002) suggested (or stated implicitly) that they had no adverse events associated with the intervention (i.e., exercise testing and (or) training); 13 (Pan et al. 1997; Agurs-Collins, Kumanyika et al. 1997; Brankston et al. 2004; Brandon et al. 2003; Castaneda et al. 2002; Cauza et al. 2005; Dunstan et al. 1997, 1998; Fuchsjäger-Mayrl et al. 2002; Giannopoulou et al. 2005; Ibañez et al. 2005; Loimaala et al. 2003; Matteucci et al. 2006) provided information on drop out that appeared unrelated to any adverse event caused by exercise (for a total of ~75% no adverse events); 6 (Bernbaum et al. 1989; Schneider et al. 1984; Banzer et al. 2004; Lemaster et al. 2003; Moore et al. 1998; Praet et al. 2008) reported minor adverse events (~13%); 2 (Mittleman et al. 1993; Schneider et al. 1992) reported major adverse events (~4%); and 4 (Faglia et al. 2002; Schneider et al. 1992; Sigal et al. 2007; Cruickshanks et al. 1995) reported major and minor adverse events (~9%).

Discussion

To our knowledge, this is the first attempt to evaluate the evidence regarding risk assessment prior to higher-intensity PA participation among persons with prediabetes or diabetes. Having a diagnosis of diabetes is frequently associated with micro- and macrovascular disease and poor cardiovascular health, particularly if metabolic control is poor. Moreover, it is not uncommon for patients to have concomitant diagnoses of both diabetes and CVD. The high prevalence of cardiovascular disease and other secondary organ damage (i.e., kidney, nerve, and retina) has long been thought to put patients with diabetes at higher risk for an adverse event associated with increased PA. As such, several organizations recommend medical screening for those persons over the age of 40 years who have prediabetes or diabetes plus any of the other 7 standard risk factors for CAD (Appendix B). According to the American Diabetes Association (ADA) (Sigal et al. 2006) and the ACSM (Albright et al. 2000), the risks of exercise include cardiovascular events, musculoskeletal injury and in some circumstances microvascular damage and (or) a worsening of metabolic control (Appendix C). Relative and absolute contraindications to exercise have also been recommended by the ADA (Gordon 2002) (Appendix D); however, we are aware of no previous attempt to quantify the risks associated with exercise in those with prediabetes or diabetes. In general, we confirm that adverse events associated with increased PA participation are a possibility, although the incidence rate appears surprisingly low.

Based on 1 large retrospective study, acute exercise (≥6 metabolic equivalents) appears to dramatically increase the likelihood of MI in persons with diabetes (Mittleman et al. 1993). In contrast, 1 large scale epidemiological study of more than 674 000 patient exercise hours in a cardiac rehabilitation setting found that diabetes had no significant impact on cardiovascular symptoms or on events (Unverdorben et al. 2007). This discrepancy in findings may be because the latter analysis was done on supervised exercise rehabilitation programs in patients who were medically cleared for exercise, while the former study was based on interviews of recent MI patients who were asked to report on the activities that they were doing in the hours before (or at the time of) the infarct. In our analysis of all the prospective studies meeting our inclusion criteria (including RCTs reporting adverse events), we found no evidence of a PA-related death and a very low incidence of nonlife-threatening adverse events. Overall, therefore, the present results appear to suggest that light- to moderate-intensity PA is a relatively safe undertaking in these individuals who are at elevated baseline risk for a number of micro- and macrovascular conditions, including CVD, neuropathy, nephropathy, and retinopathy. Nevertheless, a number of important limitations need to be acknowledged that temper this suggestion: (*i*) in the vast majority of prospective studies of persons with prediabetes and diabetes, researchers fail to document–quantify "adverse events" as a primary or even secondary outcome variable; (*ii*) a majority of studies included only subjects with few (or no) comorbidities, particularly CVD, that would likely elevate overall risk for adverse events; (*iii*) virtually all of the RCTs had CVD screening prior to participant inclusion by having patients perform a graded exercise test to examine for any signs or symptoms suggestive of myocardial insufficiency (these patients were then screened out of the study); and (*iv*) the subjects in the larger clinical trials (e.g., prediabetes cohort studies) typically perform only mild (i.e., brisk walking) or moderate-intensity exercise when unsupervised or they were supervised when they participated in more vigorous activities.

As mentioned in the introduction, the perception of risk for an adverse event associated with exercise in persons with diabetes is high. Perhaps because of this, we found that nearly all RCTs of persons with diabetes screened out participants with comorbidities by conducting a pre-exercise medical exam and then a medically supervised graded exercise stress test prior to the study intervention (i.e., exercise training). Typically, individuals were screened out of the study if they had significant CVD or other diabetes-related complications. Moreover, we found that a majority of exercise training sessions occurred under supervision with a carefully targeted exercise intensity that would likely place the participants at overall low risk for an adverse event (i.e., mild to moderate intensity). When more vigorous exercise was performed, adverse events appeared more frequently and were of more clinical concern in some (Mittleman et al. 1993; Bernbaum et al. 1989; Schneider et al. 1984, 1992; Unverdorben et al. 2007; Inoguchi et al. 2000) but not all (Balducci et al. 2004; Maiorana et al. 2002; Mourier et al. 1997; Giannopoulou et al. 2005; Loimaala et al. 2003; Matteucci et al. 2006) studies. Thus, it remains unclear if the low incidence of reported ad-

verse events documented in this analysis reflects the true safety of PA, screening-out of higher risk subjects prior to enrollment in trials, or less than optimal documentation of adverse events in many research studies. Moreover, it is unclear if more vigerous intensity dramatically increases risk for an adverse event in this patient population with a well-established high prevalence of CVD. Highlights of the documented benefits and risks of increased PA in these studies are provided below.

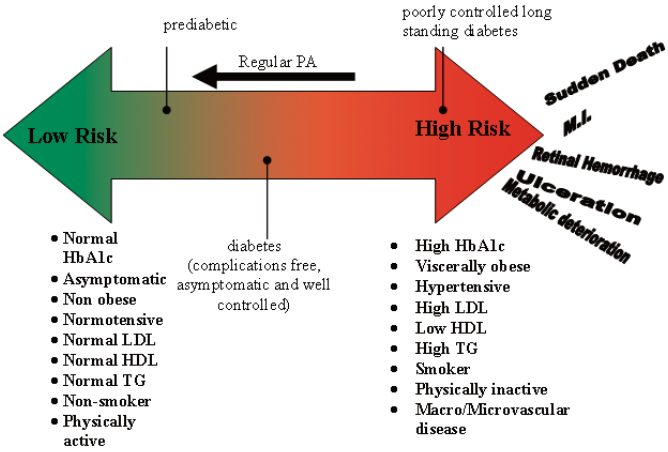
Risk stratification

Based on our analysis of the available literature at the time of our search, we propose a new risk continuum model for exercise screening for individuals with diabetes or prediabetes that could be used to determine if further medical screening is needed prior to the initiation of a new PA program (Fig. 1). This risk stratification is based on a number of well-established risk factors for CVD and micro- or macrovacular disease in persons with diabetes and the finding that exercise can be a trigger for cardiovascular symptoms–events and (or) damage to the microvasculature in patients with diabetes. Our recommendations, which focus on prediabetes and diabetes, align closely with others who have voiced concerns about the importance of screening and safety issues related to exercise in persons with these conditions (Constantini et al. 2005; Flood and Constance 2002; Chipkin et al. 2001; Albert and Bernbaum 1995; Draznin 2000; Gaudet-Savard et al. 2007; Graham and Lasko-McCarthey 1990; Bernbaum et al. 1989; Kanade et al. 2006).

As acknowledged in most reviews and recent position stands on the topic of exercise and diabetes (Sigal et al. 2004, 2006, 2008; Albright et al. 2000), the risk concerns caused by increased PA participation range from serious cardiovascular events and a worsening of diabetes-related complications, to the possibility of deterioration in metabolic control (i.e., hypoglycemia or hyperglycemia) and musculoskeletal injury. As such, each individual's unique characteristics (age, sex, disease condition, comorbid medical conditions, medications taken, diabetes related complications, etc.) should be considered when starting an exercise regimen, whether it is to be initiated by a physician, a clinical team member (nurse, dietitian, etc), or QEP.

We propose that because of their elevated baseline risk for cardiovascular disease as compared with nondiabetics, and the possibility of pre-existing microvascular complications, persons with diagnosed diabetes should be identified on the revised PAR-Q screening form. Although the risk for cardiovascular complications associated with increased PA in young persons with the disease (i.e., <40 years of age) is likely extremely low, the high likelihood of exercise associated hypoglycemia necessitates the identification of these individuals for safety reasons. Moreover, we suggest that a more detailed follow-up is needed in these people (i.e., further screening) that will help to determine their baseline risk and subsequent relative and absolute contraindications to exercise. These signs and symptoms (or risk factors) should be considered as potential identifiers on an exercise screening form to be used in the revised interactive computer-based PARmed-X. The following sections detail the evidence based recommendations for exercise screening in persons with a metabolic diagnosis.

Fig. 1. Prediabetes–diabetes risk continuum. Patients with prediabetes or diabetes are at normal to low risk for cardiovascular disease (CVD) and other diabetes-related complications if they have certain clinical characteristics, as shown. These patients are at low risk for an adverse event triggered by exercise. With elevations in mean glucose levels (as measured by HbA1c) over time, and with other certain clinical characteristics, the risks for CVD and other complications, including retinopathy, neuropathy, and nephropathy, increases. These patients are at higher risk for an adverse event axssocated with exercise, at least initially. LDL, low-density lipoprotein; HDL, high-density lipoprotein; MI, mitochondrial infarction; TG, triglycerides.



Recommendation no. 1: Persons with prediabetes and diabetes mellitus should be identified on the revised PAR-Q and PARmed-X screening tools because of their well-established risk for CVD and related comorbidities (Level 2, Grade A). Because of the elevation in risk for adverse events associated with increased PA in these individuals, further screening is needed by a QEP (or computer-based risk screening algorithm) (Level 4, Grade C). In some instances, clinical evaluation by a physician and an exercise stress test may be required before participation in vigerous activity (Level 4, Grade C).

Risks of exercise in prediabetes

Several large-scale, well-designed RCTs have been conducted showing that lifestyle intervention in adults with prediabetes attenuates the development of overt type 2 diabetes (Tuomilehto et al. 2001; Knowler et al. 2002; Kosaka et al. 2005; Pan et al. 1997). Lifestyle intervention, which includes one-on-one exercise counseling and repeated subject interactions with exercise specialists, reduces the incidence of diabetes by 44%–68%, depending on the cohort examined (Appendix E).

Despite the care in study design of several of the RCTs conducted in individuals with prediabetes, it was difficult to assess the risks of increased PA in these studies, as "adverse events" were not primary or even secondary outcome measures. As 1 lead investigator from 1 of these trials indicated to us, "adverse events were not recorded in our study since it was a lifestyle project and there was no pharmacological intervention". Two large-scale studies were of note, however, as they did make mention of adverse events. In the Diabetes Prevention Program (DPP) study of 3234 prediabetic individ-

Table 5. Typical and atypical or variant symptoms of cardiovascular disease in persons with diabetes mellitus. Modified from Hughes and White (2009).

1. Pain or discomfort in the chest, neck, jaw, arms, or other areas that may be due to myocardial ischemia (lack of adequate circulation)
2. Difficulty completing usual tasks
3. Dizziness with activity
4. Dyspnoea with minimal exertion
5. Orthopnea (breathing discomfort when not in an upright position) or paroxysmal nocturnal dyspnea (interrupted breathing at night)
6. Ankle edema (swelling)
7. Palpitations (abnormal rapid beating of the heart) or tachycardia (rapid heart beat)
8. Intermittent claudication (cramping pain and weakness in legs, especially calves, during walking due to inadequate blood supply to muscles
9. Easy fatigability
10. Lack of energy
11. Neck or jaw discomfort
12. Shoulder pain with a history similar to bursitis and related to activity
13. Upper back pain

uals (Knowler et al. 2002), reports of musculoskeletal symptoms were higher in the lifestyle group compared with the pharmacotherapy group but hospital and mortality rates were reported to be unrelated to treatment with either lifestyle or pharmacotherapy. More specifically, the study investigators reported that there were higher rates of musculoskeletal symptoms in the lifestyle intervention group (n = 1079; 24.1 events per 100 person-years) than in the placebo group (21.1 events per 100 person-years) or in the pharmachotherapy (i.e., metformin) group (20.0. events per 100 person-years). Hospitalization rates were not statistically different between groups, although they tended to be lowest in the lifestyle group (15.6% of subjects had 1 or more hospital visits over the average 2.8 year follow-up) compared with the other 2 groups (16.1% and 15.9% in the placebo and metformin groups, respectively). Death rates were low overall and were lowest in the lifestyle group (calculated to be 0.1 deaths per 100 patient-years). None of the deaths were attributed to the study interventions. Interestingly, gastrointestinal symptoms were much lower in the lifestyle group compared with either the placebo group or the pharmacotherapy group.

In the Da Qing IGT–diabetes study of 577 prediabetic subjects in China (Pan et al. 1997), there were no deaths reported in the exercise-only group, 3 deaths in the diet only group (2 cancer, 1 septicemia), 5 deaths in the exercise + diet group (1 stroke, 2 cancer, 1 accidental, 1 Crohn's disease), and 3 deaths in the control group (1 pneumonia, 2 cirrhosis). Similar to the DPP study, none of the deaths appeared linked to the PA participation, except perhaps for 1 (a stroke-related death that was not temporally linked to exercise). It is worth noting that in the Da Qing study, the activities prescribed sometimes included "very strenuous" exercise (jumping rope, playing basketball, swimming), and despite this, no other adverse events were reported.

Thus, based on the limited reports found in these 2 large-scale RCTs, it does not appear that moderate intensity exercise (home based or supervised) causes an increase in adverse events, other than musculoskeletal symptoms, in persons with prediabetes. As such, persons with prediabetes and (or) the metabolic syndrome are thought to be at the low end of the exercise and risk continuum (Fig. 1).

Recommendation no. 2: Persons with prediabetes should be screened for traditional and atypical signs and symptoms of CVD (Table 5) before initiating a new program of exercise because of their elevated baseline risk for CVD (Level 1, Grade A). If no signs or symptoms for CVD exist in persons with prediabetes or metabolic syndrome, no additional screening is required before the initiation of a new PA program, as the adverse events associated with increased PA (low to moderate intensity) in asymptomatic individuals are low (Level 2, Grade A). If typical or atypical symptoms exist, then these individuals should be sent for physician screening for CAD before starting any exercise program (Level 2, Grade A). For previously sedentary middle-aged and older individuals with prediabetes or the metabolic syndrome, high-intensity PA should be avoided, at least initially, as it may place them at elevated risk for an adverse cardiac event (acute MI, sudden death) based on their higher likelihood of having some level of baseline CVD (Level 4, Grade C).

Prediabetes in youth

The incidence of prediabetes and diabetes in youth is rising, but only very limited data are available on the benefits and risks of PA for this patient population. These studies, using a variety of methods to quantify PA and define cardiometablic disease, are consistent with the findings in adults, namely that higher levels of activity and fitness are associated with reduced risk of metabolic syndrome (Brage et al. 2004; Eisenmann 2007; Eisenmann et al. 2005; Ferreira et al. 2005; Platat et al. 2006; DuBose et al. 2007; Kelishadi et al. 2007). Currently, no RCTs reported that type 2 diabetes can be prevented by increased PA in youth, although some are currently underway (McMurray et al. 2009). No adverse events were reported or documented in the above mentioned pediatric studies.

Recommendation no. 3: Youth with prediabetes should be considered at low risk for an adverse event caused by increased PA (Level 3, Grade B). For these individuals, no additional screening is needed before the initiation of a new PA program (Level 4, Grade C).

Risks of exercise in type 2 diabetes (asymptomatic of CVD or microvascular disease)

For persons already diagnosed with type 2 diabetes, it is unlikely that increased PA can reverse their diagnosis, although some individuals may remain "medication free" for years if lifestyle intervention is successful. Although, if performed regularly, moderate intensity exercise has been shown to lower average glucose levels (i.e., HbA1c) significantly by increasing whole body insulin sensitivity. Limited data also suggest that that existing β cell mass and (or) function is increased with regular vigorous exercise (i.e., cycling for 30–40 min·day^{-1}, including at least 20 min at 75% maximum oxygen consumption, 5 days·week^{-1} for 3 months) in persons already diagnosed with type 2 diabetes (Dela et al. 2004). This has been confirmed in an animal model of the disease (Király et al. 2007). This increase in β cell mass, along with the improvement in insulin sensitivity that occurs with regular exercise likely explains the improvement in metabolic control in these patients. In line with this, several meta-analyses (Boulé et al. 2001; Snowling and Hopkins 2006; Conn et al. 2007) reported that regular aerobic exercise, in the form of walking, jogging, cycling or resistance exercise, reduces the absolute HbA1c value by about 0.6% in persons diagnosed with type 2 diabetes. Surprisingly, none of these meta-analyses attempted to quantify or comment on adverse events associated with structured exercise programs.

Rather than cause an adverse event, we found strong evidence that regular PA participation lowers the risk of having a CVD event in persons with diabetes, particularly when glycemic control is improved. Moderate or high levels of PA are associated with reduced risk of total and CVD mortality, independent of age, education, body mass index (BMI), blood pressure, total cholesterol, and smoking in persons with type 2 diabetes and the protective effect of PA was consistent in diabetic patients at any level of BMI, blood pressure, cholesterol, and smoking (Hu et al. 2005). This observation is in line with analysis performed by Hu et al. in the Nurses Health Study, which showed that among diabetic women, increased PA is associated with substantially reduced risk for cardiovascular events (Hu et al. 1999). There is also likely to be a protective effect of increased PA on microvascular complications in diabetes, perhaps as a result of improvements in glycemia, blood pressure, and dyslipidemia (Vaag 2006). It is also worth noting that, in persons with type 2 diabetes, a lifestyle intervention program with one-on-one counseling is often as effective at decreasing HbA1c as pharmacological therapy (Rydén et al. 2007).

In support of the hypothesis that increased PA does not increase CVD risk, but in fact lowers it in persons with diabetes, large cohort studies have demonstrated that both the volume of PA (Hu et al. 2001, 2005) and the level of cardiorespiratory fitness (Church et al. 2005) are related to reductions in cardiovascular events and overall mortality by as much as 70% over 15–20 years. In 1 large epidemiological study of 1263 men with type 2 diabetes, Wei et al. (2000), observed that those with low levels of fitness and the lowest PA participation were at a 1.7-fold (95% confidence interval: 1.2–2.3) greater risk of all-cause mortality compared with men who were most physically fit. Importantly, the impact of PA participation was independent of body weight as those who were of normal weight, overweight, or obese benefited to a similar extent from the protective effects of aerobic fitness.

Despite the evidence that regular exercise lowers long-term risk for CVD in persons with type 2 diabetes, it does appear that vigorous exercise possesses at least a transient increase in risk. In a retrospective investigation that the authors term "a case-crossover design", the association between strenuous physical activities and MI within the next few hours were documented (Mittleman et al. 1993). This study found that the relative risk for an MI was 5.9 in those who performed vigorous activities in the hour before the heart attack compared with those who were not performing exercise. Alarmingly, patients with diabetes (the type of diabetes was not documented) had a much higher relative risk of MI in the hour after heavy physical exertion compared with times when the same individuals were sedentary (relative risk was 18.9 in those with diabetes who had just exercised vigorously vs. the same individuals' sedentary periods). It is unclear if these individuals who had an MI during and (or) after vigorous exercise had a prior diagnosis of CAD, although one can assume that they had at least some level of baseline cardiac impairment. It is also important to note that the likelihood of sudden cardiac event was much less in the regularly active persons compared with sedentary persons and that the estimated absolute risk is quite low, even in those deemed high risk (<18 serious events per 1 million person-hours) (Mittleman et al. 1993; Thompson et al. 2007).

Previously, a number of cautious PA clearance recommendations have been proposed for persons with diabetes by professional organizations (Appendix F). According to most of these recommendations, if a person presents with diabetes and wishes to initiate a new exercise program, he or she is recommended to get medical clearance and perhaps a cardiac stress test. We found little evidence that moderate intensity exercise or even an exercise stress test places otherwise healthy individuals with diabetes at increased risk for any cardiovascular events. We found 21 RCTs that had some mention of adverse events (or lack thereof) associated with exercise in persons with diabetes who were largely free of CVD (i.e., subjects were prescreened). Moreover, the event rate (or subject withdrawal rate because of a cardiac condition) was often similar between subjects with diabetes and the controls (i.e., nondiabetic) (Unverdorben et al. 2007; Banzer et al. 2004). However, these studies were generally of relatively short duration (either graded exercise stress tests, or short duration prospective studies lasting weeks to months) and are likely underpowered to identify rare adverse events such as sudden cardiac death, MI, or stroke.

Similar to our findings, a Cochrane review by Thomas et al. (2006) documented only a handful of comments about adverse events in the 14 RCTs that met their inclusion criteria for RCT training studies and glycemic control in persons with diabetes. As pointed out in that review, none of the studies stated that adverse events were an outcome variable that had standardized assessment. Some studies, however, stated explicitly that there was a lack of "serious adverse effects" or that there were "no exercise-induced injuries" in the intervention group. For example, Baldi and Snowling (2003) reported that there were no complaints or injuries after some expected muscle soreness in the early stages, while Yeater et al. (1990) reported an absence of orthopaedic complaints or

injuries. Praet et al. (2008), found only 1 "overload injury" and minor episodes of hypoglycemia in 36% of subjects during aerobic and resistance training in long-standing, insulin-treated patients with type 2 diabetes.

Hypotension is another possible event that can occur with exercise and its occurance is thought to be a marker of autonomic neuropathy in persons with diabetes. Schneider et al. (1984), documented 8 cases of asymptomatic and symptomatic hypotension following maximal exercise testing when mildly obese diabetic subjects ($n = 20$) were in an untrained state. However, no orthostatic changes occurred during or following training and no subjects experienced clinically relevant visual, renal, or neurological deterioration (Schneider et al. 1984). Mourier et al. (1997) reported that the participants' compliance and tolerance for the training regime (intense cycling 3 times per week for 2 months) were good and that no exercise bout was stopped for medical reasons. Similarly, we found several other studies that stated explicitly that there were no adverse events as a result of exercise (Gaudet-Savard et al. 2007; Balducci et al. 2004, 2006; Honkola et al. 1997; Ozdirenç et al. 2004; Tokmakidis et al. 2004; Tudor-Locke et al. 2004; Agurs-Collins et al. 1997; Castaneda et al. 2002; Giannopoulou et al. 2005; Ibañez et al. 2005; Loimaala et al. 2003; Cauza et al. 2006). Other studies reported on the efficacy of training and made no reference to any adverse effects in the exercise group often stating that drop out occurred for non-medical reasons or reasons unrelated to exercise (Dunstan et al. 1998, 2002; Dela et al. 2004; Cuff et al. 2003; Raz et al. 1994; Rönnemaa et al. 1986; Tessier et al. 2000; Tsujiuchi et al. 2002; Wing et al. 1988). With all of the above mentioned studies in which risk for adverse events were low, the subjects with type 2 diabetes did not have any other major comorbidity. As such, we feel that a major selection bias has occurred that precludes us from concluding that increased PA is without risk for serious adverse events in persons with type 2 diabetes.

Less is known about the benefits and risks associated with resistance training in type 2 diabetes, although the reports of risks associated with this form of exercise are mainly on musculoskeletal discomfort (Sigal et al. 2007; Dunstan et al. 1998, 2002). A recent review–meta-analysis by Eves and Plotnikoff (2006) highlights the beneficial effects of resistance training on glucose homeostasis, insulin sensitivity, body composition, and lipid profile. This analysis failed to comment on any safety issues or adverse events associated with the activity. In 1 recent RCT conducted by Sigal et al. (2007), a combined aerobic and resistance training regimen improved glycemic control (as measured by HbA1c) better than either exercise regimen alone, suggesting that a combined aerobic and resistance training prescription may be the best prescription for improved HbA1c and lipid profile. In that study, the reduction in HbA1c in men and women that performed resistance and aerobic exercise regularly over a period of 22 weeks was 0.97% compared with nonexercising controls. This study is also important as it is one of the few that thoroughly documented adverse events associated with the treatment intervention. In that study, the incidence of adverse events associated with exercise were high (38% of exercising subjects compared with 16% of control subjects reported at least 1 adverse event during the 26-week study), but these were mostly related to transient musculoskeletal discomfort or minor injury. None of the adverse events attributed to exercise were lasting or life threatening. However, prior to enrollment in this study, subjects were screened with a maximal exercise test with ECG monitoring, and subjects with advanced retinopathy, neuropath,y or nephropathy were excluded. Thus the study population was probably at lower cardiovascular risk than the average middle-aged or older person with diabetes.

Our research findings support the current recommendations from the ADA that indicates that medical screening be considered, along with a graded exercise stress test with ECG monitoring, before undertaking aerobic PA with an intensity exceeding the demands of everyday living (more intense than brisk walking) in previously sedentary diabetic individuals whose 10-year risk of a coronary event is >10% based on the UKPDS risk engine (Stevens et al. 2001). The UKPDS risk engine can only be used for those individuals diagnosed with type 2 diabetes, however. Although we did not find any evidence that low- to moderate-intensity PA places individuals at more risk, it is clear that these persons are at high risk of having CVD and that vigorous exercise is a potential trigger of adverse events. If the UKPDS risk engine is not accessible, or if not all of the questions in the risk engine can be answered, Sigal et al. recommended that the >10% risk would correspond approximately to meeting any of the following criteria (Sigal et al. 2004).

- Age >40 years, with or without CVD risk factors other than diabetes
- Age >30 years and
  - Type 1 diabetes or type 2 diabetes of >10 years duration
  - Hypertension
  - Cigarette smoking
  - Dyslipidemia
  - Proliferative or pre-proliferative retinopathy
  - Nephropathy, including microalbuminuria
- Any of the following, regardless of age:
  - Known or suspected coronary artery disease, cerebrovascular disease, and (or) peripheral vascular disease
  - Autonomic neuropathy
  - Advanced nephropathy with renal failure

Recommendation no. 4: Middle-aged and older persons with type 2 diabetes should be considered at moderate to high risk for CVD and sudden cardiac death (Level 1, Grade A). Because of their elevated risk for MI associated with vigorous PA, rigorous screening should be conducted before the onset of a new PA program more vigorous than brisk walking (Level 3, Grade A). All persons with type 2 diabetes who have signs or symptoms suggestive of CVD, or a >10% risk of having a cardiovascular event based on the UKPDS Risk Engine, should seek medical approval before initiating a new PA program that includes activities more vigorous than brisk walking (Level 4, Grade C). No resrictions should be placed on otherwise asymptomatic patients with type 2 diabetes for light to moderate activities (Level 4, Grade C).

Risks of exercise in type 2 diabetes (symptomatic of CVD or with diagnosed CVD)

Based on 1 case-crossover design study (Mittleman et al. 1993), it appears that vigorous exercise increases risk for ma-

jor cardiovascular events in persons with diabetes compared with sedentary behavior, particularly if they were unaccustomed to the activity. We found evidence from other studies published on cohorts of diabetic patients undertaking cardiac rehabilitation that also suggests the risks of an adverse event are significant in those with diabetes who have underlying diabetes-related complications. For example, Banzer et al. (2004), reported that subjects with diabetes withdrew considerably more from PA participation (62% dropout rate) than nondiabetic subjects because of an exacerbation of medical problems, although cardiac conditions precluded program completion at a similar rate in both groups (9.8% of diabetics vs. 8.5% of nondiabetics). In a 10-year experience with an exercise-based outpatient lifestyle modification program, Schneider et al. (1992) found that 12% of participants had an exercise-related injury that precluded exercise for at least 1 week, although admittedly this percentage is likely not much different from what would be observed in nondiabetic populations. Furthermore, ~10% of patients with retinopathy developed retinal hemorrhage or minor foot lesions over a 10-year follow-up. Another key observation from all of these studies is that exercise adherence is lower in patients with complications from diabetes compared to those without diabetes and this may be related to an increase in adverse events in the former group.

Recommendation no. 5: For persons with type 2 diabetes who have been diagnosed with, or have symptoms of, CVD, peripheral artery disease, and (or) microvascular complications (retinopathy, nephropathy, peripheral neuropathy, autonomic neuropathy), an initial medical assessment should be performed before initiating any new program of PA (Level 4, Grade C). For these same individuals, vigorous aerobic exercise should be avoided, unless they have been cleared by their physician after a medical assessment that includes an exercise stress test and ECG evaluation (or alternative imaging) (Level 4, Grade C). In people with inducible coronary ischemia, following medical clearance, PA programming should ideally be performed under appropriate supervision (e.g., cardiac rehabilitation model) to help maintain a low risk for CVD mortality and morbidity in these high-risk individuals (Level 4, Grade C).

Risks of exercise in type 1 diabetes

In contrast to the beneficial effects of exercise on glycemic management in persons with type 2 diabetes, most clinical trials evaluating exercise interventions in people with type 1 diabetes have not demonstrated a positive effect of exercise on glycemic control (Laaksonen et al. 2000). Nonetheless, in a large type 1 diabetes cohort study, it was found that 7-year mortality was ~50% lower in those reporting ≥ 2000 kcal of weekly exercise (equivalent to ≥ 7 h·week^{-1} of brisk walking) compared with those reporting <1000 kcal of PA participation per week (Moy et al. 1993). As highlighted in the recent Canadian Diabetes Association (CDA)'s Clinical Practice Guidelines on PA participation and diabetes, regular aerobic exercise increases cardiorespiratory fitness, reduces the risk of diabetes-related complications, and improves psychosocial status in persons with type 1 diabetes (Sigal et al. 2008).

Many individuals with type 1 diabetes develop some microvascular (retinopathy, neuropathy, nephropathy) and (or) macrovascular complications about 10–15 years after diagnosis (Nathan et al. 2009). Long-term complications, such as peripheral neuropathy, are less likely in persons with type 1 diabetes who are more physically active. In a RCT using 4 years of supervised exercise (4 times per week at 50%–85% heart rate reserve) with both type 1 (n = 19) and type 2 (n = 57) patients, the percentage of diabetic patients that developed motor neuropathy and sensory neuropathy during the 4 years of the study was significantly higher in the nonexercising control group than the exercise group (17% vs. 0% for motor neuropathy and 29.8% vs. 6.45% for sensory neuropathy) (Balducci et al. 2006). Importantly, the authors reported that there were no adverse events associated with the 4-year intervention.

Surprisingly, the risk for CAD in persons with long standing type 1 diabetes appears to be as high as those of the same age with type 2 diabetes even though the former are generally less likely to be overweight–obese and insulin resistant, and less likely to have hypertension or dyslipidemia (Laing et al. 2003). This finding supports the hypothesis that hyperglycemia is a major contributor to cardiovascular disease progression (Milicevic et al. 2008). Persons with type 1 diabetes are at very high risk of having CAD with ~50% of patients having clinically significant CAD by the age of 55 years (Juutilainen et al. 2008), although recent data suggests that the prevalence of CVD in those with type 1 diabetes may be much less since the initiation of intensive insulin therapy (Nathan et al. 2009). The level of diabetes control predicts CVD mortality rate in persons with type 1 diabetes, with any HbA1c over 7.0% elevating risk (Juutilainen et al. 2008). In 1 example of how atypical risk factors predict CAD, angiographic studies of asymptomatic patients with type 1 diabetes and renal failure have revealed that ~50% of these individuals have significant CAD (Janand-Delenne et al. 1999). Autonomic neuropathy is also highly predictive of CAD in persons with diabetes as >50% of patients who have the complication die, mostly from sudden death, within 5 years (Ewing et al. 1980). Reports of CVD events associated with exercise in those with type 1 diabetes are uncommon, perhaps in part because of the small number of exercise studies conducted in this patient population. Moreover, the studies that have been conducted on this patient population are typically done on young individuals free of micro- and macrovacular complications.

We found that one of the most common adverse events associated with exercise in persons with type 1 diabetes is hypoglycemia. For example, hypoglycemia during just one 75-min intermittent exercise session occurred in 86% of children starting the exercise with normal glucose levels (Tansey et al. 2006). In studies of adults with type 1 diabetes who had continuous glucose monitoring, nearly all active persons were shown to develop exercise-associated hypoglycemia within 12–24 h of recovery (Iscoe et al. 2006, 2008) . In a multicentered study of 50 youth with type 1 diabetes, postexercise hypoglycemia occurred in 26% of subjects after just 1 typical exercise bout, compared with only 6% in the same children after a sedentary day (Tsalikian et al. 2005). In most individuals with type 1 diabetes, the severity of hypoglycemia is mild and a number of strategies exist to help prevent hypoglycemia associated with exercise (Sigal et al. 2008; Robertson et al. 2008). In 1 study of 10 adolescents with type 1

diabetes, all subjects completed 12 weeks of endurance training and calisthenics without injury or illness (Mosher et al. 1998). Importantly, Lehmann et al. (1997) found the frequency of hypoglycemic events decreased with physical training.

Recommendation no. 6: No exercise restrictions should be placed on previously sedentary persons with type 1 diabetes under the age of 30 years (or over the age of 30 years but diabetes duration of <10 years) and who are free from symptoms of CVD and diabetes-related complications as the risks for clinically significant adverse events (except for hypoglycemia) are low (Level 3, Grade C). Individuals with signs and symptoms of CVD (Table 5) should be sent for CVD screening by a physician before the initiation of a new exercise program more vigorous than brisk walking. (Level 3, Grade C). For all individuals with type 1 diabetes, vigilance is required to limit PA-associated hypoglycemia in these individuals, as the risk for this adverse event is high (Level 2, Grade A).

Recommendation no. 7: For previously sedentary persons with type 1 diabetes over the age of 30 years (and with diabetes duration ≥ 10 years), or with any diabetes related complications (micro- or macrovascular), exercise programming of activities more vigorous than walking should be suspended pending medical follow-up that may include exercise stress testing for the evaluation of CVD (Level 4, Grade C).

Absolute and relative contraindications to exercise

Signs and symptoms of coronary insufficiency

In persons with prediabetes or diabetes, symptoms of chest pain or pressure are considered contraindications to exercise until further investigation is conducted. Persons with diabetes may have other atypical symptoms of myocardial insufficiency (Table 5), including dyspnea on exertion or unexplained gastrointestinal complaints that would also constitute a contraindication to exercise (Hughes and White 2009). In addition, if individuals report having had a previous MI or if they have been told they have myocardial ischemia (e.g., resting ST segment abnormalities), then an exercise stress test is advisable prior to initiating an exercise program. For persons with diabetes, an increased risk of CAD is associated with the presence of smoking, hyperlipidemia, cardiomegaly, and congestive heart failure (Hughes and White 2009). In support of this, a multivariate analysis that included a history of prior MI, 12-lead ECG abnormalities, smoking and hyperlipidemia showed that diabetes itself had an additional effect on the likelihood of having CAD (Pryor et al. 1983).

Since those with diabetes who are more physically active have much less risk for a cardiovascular event than those with disease who are sedentary (Gill and Malkova 2006), the general consensus is that the risks of exercise are outweighed by the numerous benefits, as long as certain precautions are taken. It is important to note that not all persons with type 1 should be considered at high risk for CVD, particularly if they are under good glycemic control (Konduracka et al. 2007). For patients with type 2 diabetes, long-term maintenance of glycemic control (as measured by HbA1c level) is also protective for the development of CVD (Standl et al. 1996), although some evidence indicates that a near normal HbA1c (6.4%) through the use of thiazolidinediones might actually increase risk of death in type 2 diabetic patients who have CVD (Gerstein et al. 2008). Thus, healthy lifestyle behaviors and intensive pharmacological therapy that promotes good glycemic control should be an early goal for all persons with diabetes, prior to their significant development of CVD, to help minimize their risk of developing early CVD mortality and morbidity.

Hypertension and hypotension

The most feared risk of initiating a PA regimen is sudden death secondary to an arrhythmia or an ischemic event. Sudden death may be more likely to occur when underlying CAD is undiagnosed, and undiagnosed CAD is particularly common in persons with diabetes mellitus (Schneider et al. 1992). As described above, the risk of an adverse cardiac event following vigorous exercise is particularly high in persons with diabetes compared with the same individuals when they have not exercised in the previous hour (Mittleman et al. 1993).

It may be that the increased adverse events associated with vigorous PA in persons with diabetes are related to their inappropriate blood pressure response to exercise. Indeed, autonomic dysfunction frequently occurs in persons with diabetes 10–15 years following disease diagnosis (Keen 1994). The clinical manifestations of cardiovascular autonomic neuropathy include exercise intolerance, intraoperative cardiovascular lability (i.e., increased cardiovascular morbidity and mortality during surgery), orthostatic hypotension, painless myocardial ischemia, and increased risk of mortality (Maser and Lenhard 2005). Although studies have yet to be conducted that examine the risks of PA in patients with autonomic neuropathy, QEPs should be aware that exercise regimens may need to be altered and there is an increased need for surveillance for cardiac ischemia (Maser and Lenhard 2005) and for cardiovascular autonomic neuropathy (Vinik and Erbas 2002). These alterations should include a prolonged warm-up and cool-down phase (10 min each), a lower intensity conditioning phase (20–60 min at a rating of perceived exertion of 10–13 on a 20-point scale or 3–6 on a 10-point scale) and frequent blood pressure and heart rate monitoring. In addition, using stationary cycling may be preferable over weight-bearing exercise that requires standing or walking as cycling does not provoke a hypotensive response in these higher risk individuals (Bernbaum et al. 1989)

Because of autonomic dysfunction in persons with diabetes, there may be an exaggerated hypertensive response to exertion (Vinik and Erbas 2002; Blake et al. 1990). Moreover, persons with diabetes also appear to be at increased risk for exaggerated postexercise hypotension particularly if they have diabetes related complications (Moore, Painter, Brinker et al. 1998), which may place them at increased risk for an adverse event either during or immediately after exercise (Bernbaum et al. 1989; Faglia et al. 2002; Schneider et al. 1984, 1992; Unverdorben et al. 2007; Banzer et al. 2004). It is also important to note that the hypertensive response to exercise in persons with diabetes might put them at risk for other adverse events including microvascular damage to the kidney, retina, or cerebral vessels, although the evidence for this is not overwhelming (Schneider, Khachadurian, Amorosa et al. 1992) (Table 4). Nonetheless, caution about the exercise prescription is warranted.

Recommendation no. 8: Patients with type 1 or type 2 diabetes who have autonomic dysfunction or polyneuropathy should be allowed to perform ligh-t to moderate-intensity PA without restriction (Level 4, Grade C). Vigorous PA should be avoided in these patients until they have been evaluated medically and cleared for such participation (Level 4, Grade C). The evaluation will in many cases include an exercise stress test evaluation.

Microvascular disease

Retinopathy

Retinopathy is a common microvascular complication of diabetes that can lead to blindness. Hyperglycemia and the associated increase in free radicals appear to damage the retinal vessels over time, causing impaired blood circulation and leakage of blood and blood products into the retina (termed background retinopathy) (Jawa et al. 2004). Without aggressive treatment of hyperglycemia, retinal vessels undergo ultrastructural damage, macular edema, new vessel growth (termed proliferative retinopathy), and eventually retinal hemorrhage causing blindness. The effect of exercise on retinal damage in those with either background or proliferative retinopathy is unclear, but there is concern that increases in blood pressure and (or) jarring movements at the latter stages of disease progression may facilitate retinal hemorrhage (Aiello et al. 2001). During a 10-year exercise-based outpatient program for persons with diabetes (both type 1 and type 2) who had multiple complications at baseline, there was a 10% occurrence of retinal hemorrhage temporally related to exercise (3 out of 30 patients who had baseline retinopathy) (Schneider et al. 1992). It is important to note that events occurred only when the exercise was more vigorous than what had been prescribed by their exercise professional (Schneider et al. 1992) and the occurrences of retinal hemorrhage in non PA individuals with retinopathy was not provided for comparison.

In contrast to the 1 study mentioned above (Schneider et al. 1992), 2 prospective cohort studies in humans with existing retinopathy did not show an increased risk of retinopathy progression or of vitreous hemorrhage with increased participation in team sports and exercise in this population (Bernbaum et al. 1989; Cruickshanks, Moss, Klein et al. 1992, 1995). Several cross-sectional (Cruickshanks et al. 1992; Samanta et al. 1991; Kriska et al. 1991) and 2 retrospective observational studies (Orchard et al. 1990; LaPorte et al. 1986) were found that showed no association between PA participation and the risk of worsening retinopathy in persons with type 1 diabetes. Some evidence from 1 of these cross-sectional studies even supports the notion that increased PA participation in sport might delay the development of retinopathy, at least in females (Cruickshanks et al. 1992). These limited data suggest that PA participation does not influence the risk of developing diabetic retinopathy if exercise is performed appropriately (i.e., not causing an excessive hypertensive response). Nonetheless, because of the fear that an increase in blood pressure associated with heavy exercise might cause retinal hemorrhaging and because prolonged exercise may increase growth hormone levels, which are associated with the development of retinopathy (Jawa et al. 2004), persons with advanced retinopathy are frequently advised to avoid strenuous activities that increase blood pressure above 170 mm Hg systolic (Aiello et al. 2001).

In a National Institutes of Health consensus panel report (National Institutes of Health 1987) it was stated that "activities that require straining and breath holding" increase ocular risk of retinal detachment and vitreous hemorrhage because of elevations in blood pressure. As such, they do not endorse certain activities, such as weight lifting, for persons with diabetes who had evidence of retinopathy. This expert opinion-based recommendation is controversial, however, since resistance exercise using moderate weight training (e.g., 3 sets of 8RM of the major muscle groups) appears to be associated with lower blood pressure response compared to typical aerobic activities such as stair climbing (Sigal et al. 2004). Given the preceding evidence, authors of various organizations (Sigal et al. 2004, 2006; Albert and Bernbaum 1995; Graham and Lasko-McCarthey 1990; Aiello et al. 2002) have generally recommended moderate intensity exercise (aerobic and resistance) but advised against vigorous exercise (aerobic and resistance) for those with severe nonproliferative or proliferative retinopathy and severe non-proliferative retinopathy.

Recommendation no. 9: The status of retinopathy should be assessed by an ophthalmologist or experienced optometrist before starting a new PA program in patients with diabetes (Level 4, Grade C). In persons with diabetes (either type 1 or type 2) who have nonproliferative retinopathy, no additional PA restrictions are required for exercise programming (Level 3, Grade B). Those with severe nonproliferative or proliferative retinopathy should have a clinical evaluation, which may include a graded exercise test with ECG and blood pressure monitoring, before starting a program of PA more vigorous than brisk walking or cycling (Level 4, Grade C). After appropriate screening, persons with severe diabetic nonproliferative retinopathy or proliferative diabetic retinopathy should avoid strenuous PA (aerobic or resistance) that raises blood pressure > 170 mm Hg systolic, particularly when vitreous hemorrhage and (or) fibrous retinal traction is present (Level 3, Grade B). The suspension of exercise should occur pending further retinal screening if there is a sign of worsening preproliferative or proliferative retinopathy because of the elevated risk for traction retinal detachment or vitreous hemorrhage (Level 4, Grade C).

Kidney disease

Nephropathy (kidney disease) that progresses to end-stage renal disease is a complex microvascular complication of diabetes that has a detrimental impact on a number of other systems, including muscle, cardiovascular, respiratory, nervous, gastrointestinal, urogenital, and hematological systems. Advanced nephropathy is categorized by an increase in protein loss in the kidney (proteinuria). We found no evidence that PA participation worsens resting proteinuria in persons with type 1 or type 2 diabetes (Garg et al. 1995; Groop et al. 1990). Despite hypothetical adverse effects of increased proteinuria immediately after exercise, existing data show no progression of nephropathy with exercise and, in fact, increasing PA may decrease existing albuminuria (a type of proteinuria) (Fredrickson et al. 2004; Lazarevic et al. 2007). In cross-sectional studies, increased PA is associated with a decreased risk of developing nephropathy (Kriska et al. 1991; Wadén et al. 2008).

Although evidence does not support the avoidance of PA in persons with diabetes and known kidney disease, some precautions are warranted (Mogensen 2002; Headley et al. 2002). Those with early nephropathy, who typically have low exercise tolerance, should probably avoid vigorous exercise, although mild to moderate intensity exercise is thought to be beneficial (Mogensen 2002). Individuals with end-stage renal disease have very low exercise tolerance, low aerobic capacity ($\dot{V}O_{2\,max}$ <20 mL·kg^{-1}·min^{-1}), decreased cardiac output, blunted heart rate response to exercise, anemia and decreased O_2 extraction (Evans and Forsyth 2004). As such, these individuals need special care when prescribing exercise and should be under close supervision. Cardiovascular complications are also common in individuals with nephropathy, although little evidence exists that exercise triggers any adverse events (Moore et al. 1998; Painter 1988; Painter et al. 2002, 2003). As special care may be needed in these individuals with advanced disease, including erythropoietin administration (Moore al. 1998; Painter et al. 2002), supervised exercise programs are recommended.

Recommendation no. 10: Persons with diabetes mellitus (either type 1 or type 2) who have end-stage renal failure should undergo medical screening prior to initiating a PA program (Level 4, Grade C). Following clinical evaluation, light- to moderate-intensity PA can be conducted if early nephropathy exists, but vigorous exercise should be avoided (Level 4, Grade C). In those with advanced nephropathy and are undergoing dialysis, exercise testing should be performed before the initiation of an exercise program that is more vigorous than walking, but both mild-aerobic and low-intensity exercise is still not contraindicated when under appropriate supervision (Level 4, Grade C).

Sensorimotor polyneuropathy

Diabetic peripheral polyneuropathy (i.e., disease of, or damage to, nerves outside of the brain) develops within 10 years of the onset of diabetes in 40% to 50% of people with type 1 or type 2 diabetes (Nathan et al. 2009). Polyneuropathy occurs in several motor and sensory nerves and may be associated with movement difficulties, weakness, pain, and the loss of peripheral sensation that is linked to increased risk of ulceration and poor wound healing causing amputation. Both somatic and autonomic neuropathy can occur and may require referral to a specialist experienced in managing the affected body systems. Several aspects of safety are of consideration for people with neuropathy, including their cardiovascular impairment during exercise, their risk of foot ulcerations, and their risk of falls. Unfortunately, clinical trials measuring the adverse events associated with exercise in persons with neuropathy are limited.

Increased PA participation appears to dramatically lower the risk of developing peripheral neuropathy (Balducci et al. 2006; Kriska et al. 1991). We found no evidence that exercise causes a worsening of diabetic neuropathy. In fact, 2 studies observed that increased PA participation actually decreased the risk of foot ulceration in persons with diabetes who were also diagnosed with neuropathy (Lemaster et al. 2003; Armstrong et al. 2004). However, some laboratory-based evidence suggests that abrupt increases in activity may increase the short-term risk of ulceration because of increased plantar pressures (Kanade et al. 2006; Lemaster et al. 2003).

Recommendation no. 11: Persons with diabetes mellitus (either type 1 or type 2) who have severe peripheral neuropathy should engage in PA under appropriate supervision and with proper footwear to lower their risk of injury from falls and development of foot ulcers (Level 4, Grade C).

Worsening hyperglycemia

Currently, no studies have investigated if there is a minimum level of glycemic control in diabetes, as measured by HbA1c, which is needed to ensure patient safety before starting an exercise program. In patients with type 1 diabetes, acute exercise can sometimes increase blood glucose levels, although this effect is largely transitory if they are on intensive insulin therapy (Riddell and Perkins. 2006). Typically, individuals with type 2 diabetes are encouraged to initiate PA immediately after diagnosis to improve glycemic management, in the absence of advanced cardiovascular disease requiring surgical intervention (e.g., bypass, angioplasty).

Recommendation no. 12: No PA restrictions should be placed on individuals recently diagnosed with diabetes (either type 1 or type 2) as long as blood glucose management strategies have been initiated by their physician (Level 4, Grade C). Individuals with excessive hyperglycemia (fasting blood glucose >15 mmol·L^{-1}) and elevated ketone levels in their urine (ketonurea) should refrain from initiating vigorous exercise until glycemic control is re-established (Level 4, Grade C).

The utility of medical screening and exercise stress tests

Because of the close association between metabolic dysregulation and cardiovascular disease, many organizations recommend medical screening and a graded exercise stress test prior to initiating an exercise training regimen more vigorous than walking (Sigal et al. 2004, 2006, 2008; Albright et al. 2000). This screening is for the assessment of conditions that might contraindicate certain types of exercise because of a predisposition towards injury (e.g., severe cardiovascular disease, severe autonomic neuropathy, severe peripheral neuropathy, or proliferative retinopathy). As such, these complications are considered relative contraindications to certain types of exercise that require treatment prior to the initiation of any vigorous exercise program. A description of the various exercise intensities can be found elsewhere (Warburton et al. 2009).

Our systematic review revealed that adverse events are not a well-documented outcome measure in studies conducted on patients with metabolic disease. Only in 1 captured paper were adverse events rigorously monitored and reported during an exercise intervention (Sigal et al. 2007). Even in this well-designed study, however, high-risk subjects with diabetes were screened out prior to randomization, which likely results in under-representation of the true risk for adverse events associated with PA participation in persons with type 2 diabetes. This common screening process (i.e., a graded exercise stress test with signs or symptoms of CVD being an exclusion criterion) in RCTs prior to initiating an exercise intervention makes it difficult to assess the risk in more advanced cases of complicated diabetes.

The ACSM and the American Heart Association (AHA) recommends that pre-exercise screening be done, using non-invasive exercise testing, for all asymptomatic individuals (i.e., those who have not been diagnosed with a medical condition) who also have the presence of 2 or more coronary risk factors, including elevations in fasting glycemia (Appendix B). We feel that these recommendations are particularly conservative and may, in fact, be a barrier to exercise participation in individuals most in need. They also recommend screening and an exercise stress test for patients >40 years of age with only 1 risk factor for CVD. Based on a risk calculator (http://www.exrx.net/Calculators/RiskClass.html), the ACSM recommends medical examination and a medically supervised exercise stress test before participation in an exercise program for anyone with diabetes (type 1 or 2) since they are deemed "high risk" for CVD (Anonymous 2009). In fact, in 1 case study presented in their most recent text (Anonymous 2009), the ACSM classified a hypothetical patient as "high risk" — a 36-year- old nonsmoker (BMI = 18.5 $kg \cdot m^{-2}$) living with type 1 diabetes since the age of 7 years but with no major signs or symptoms of CVD — and thus required physician screening before engaging in PA programming. This is particularly surprising as the hypothetical patient is already physically active (teaching aerobic classes 3× per week) and walks approximately 45 min 4× per week. Similarly, since diabetes is considered a risk factor for CAD, according to AHA (Balady et al. 1998), all persons with diabetes over the age of 40 years would need an exercise stress test before initiating an exercise program. Because of the demographic distribution of persons with diabetes in Canada, and using the ACSM–AHA recommendation, that would mean that ~1.5 million persons with diabetes would require stress testing if they were to decide to become significantly more active. Since obesity is also a major risk factor for both diabetes and CAD, then an additional 5 million Canadians would require exercise evaluation if all of these individuals intended on becoming much more physically active. Based on a conservative estimate of $250 per exercise stress test, this would cost the Canadian health care system about $800 million if half of these individuals were to become much more physically active. It is also important to note that clinical stress testing has only a moderate sensitivity and specificity for the diagnosis of myocardial ischemia and coronary artery disease in healthy persons and in persons with diabetes (Hughes and White 2009). Because of the obvious impracticality of this endeavor, both in terms of cost and availability of testing expertise and equipment, these prior recommendations raise concern as they may unnecessarily delay exercise participation in the groups that may benefit the most. We offer an alternative approach to screening prior to the initiation of an exercise program in persons with prediabetes and diabetes.

One accepted method of determining coronary heart disease and stroke risk in persons with type 2 diabetes, based on a large cohort investigation, is the UKPDS risk engine that categorizes individuals into low, moderate, and high risk for these conditions (http://www.dtu.ox.ac.uk/riskengine/index.php). For this, information about age, gender, duration of diabetes, HbA1c, blood pressure, cholesterol, etc., is entered into the risk engine that provides risk estimates and 95% confidence intervals for individuals with type 2 diabetes (who do not have diagnosed heart disease), for nonfatal and fatal coronary heart disease, and nonfatal and fatal stroke. This risk engine could be useful in deciding if an individual with type 2 diabetes is at high risk for CVD and should thus be referred for stress testing prior to beginning a vigorous exercise program.

We recommend that the UKPDS risk engine be used to calculate CVD event risk in otherwise healthy persons diagnosed with type 2 diabetes before initiating an exercise program more vigorous than brisk walking (see Recommendation no. 4). We also recommend that medical screening, including an exercise stress test, be performed prior to the initiation of a PA program more vigorous than walking if the individual's 10-year CVD event risk is at or above 10%. These recommendations are in line with the most recent published standards of care suggesting that diabetic individuals with more than a 10%, 10-year risk for CVD by the UKPDS risk engine calculator should consider exercise stress testing to screen for latent ischemia before initiating vigorous aerobic exercise regimens that exceed the "demands of everyday living" (Rydén et al. 2007).

New PAR-Q–PARMed-X screening process for persons with prediabetes and diabetes mellitus

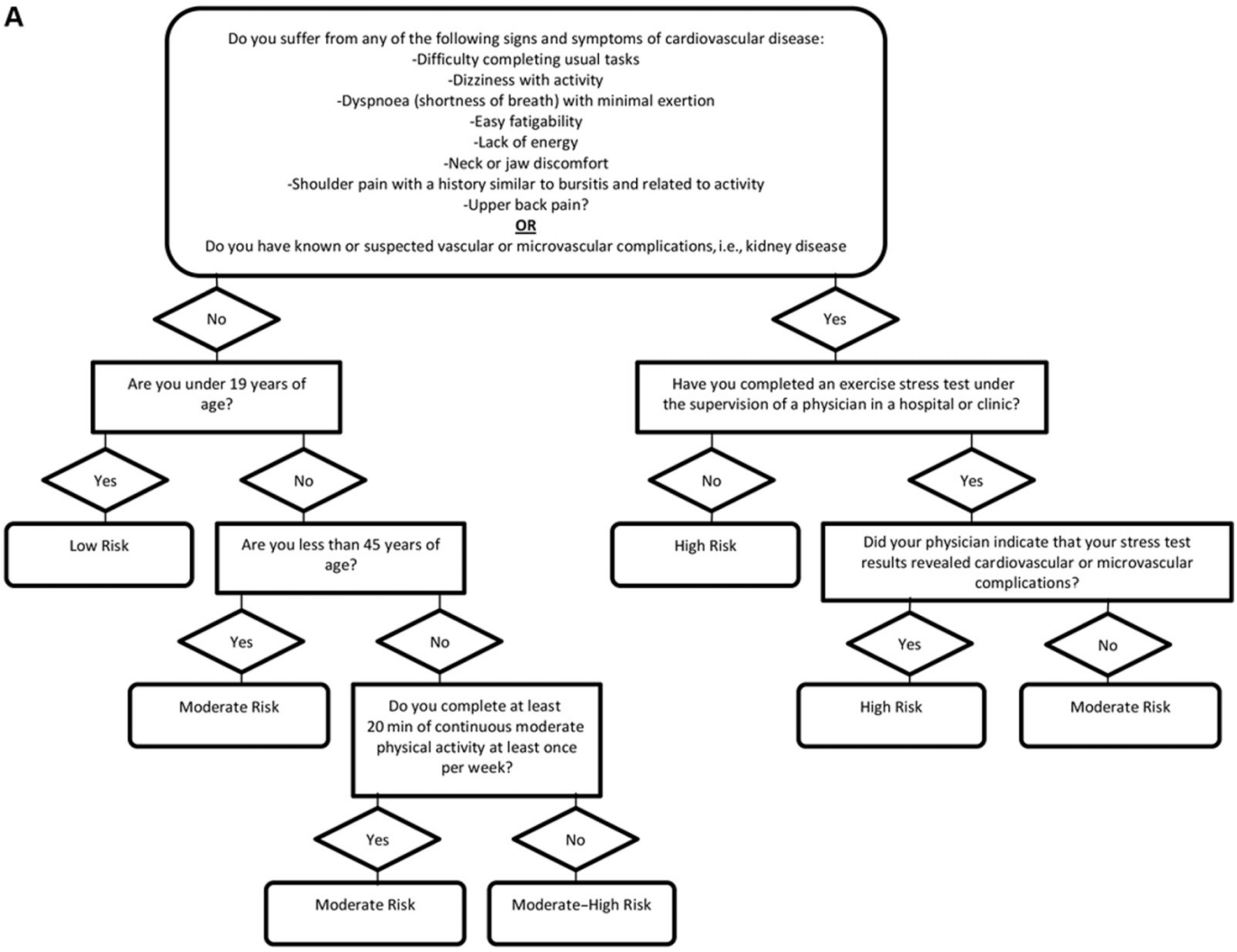
Based on our evidenced-based analysis of all published adverse events associated with exercise in persons with prediabetes, type 1 diabetes, and type 2 diabetes, we propose a new PAR-Q–PARMed-X screening process and decision tree for exercise screening for individuals with these common metabolic diseases (Fig. 2). For a great majority of individuals with prediabetes and diabetes, low- to moderate-intensity activity appears safe and effective for lowering the risk of developing diabetes-related complications. Low- to moderate-intensity PA also appears safe for individuals with diabetes who have existing diabetic microvascular complications, although vigorous-intensity activity, high-impact exercise, or heavy weight-bearing exercise may lead to adverse outcomes in those with pre-existing conditions. Exercise stress testing is recommended, however, for all persons with type 2 diabetes who have an elevated 10-year risk for a CVD event, based on the UKPDS risk engine, prior to initiating a new program of exercise more vigorous than walking. For persons with type 1 diabetes over the age of 30 years and diabetes duration >10 years, an exercise stress test is also recommended if they have not been PA previously. The need of an exercise stress test may not be warranted prior to the initiation of a moderate-intensity exercise regimen in otherwise healthy individuals with diabetes, however, should be considered prior to initiating a program of vigorous exercise in those unaccustomed to it.

For individuals who have type 1 or type 2 diabetes who are also diagnosed with advanced peripheral neuropathy or with proliferative retinopathy, vigorous aerobic and heavy resistance exercise is contraindicated, although mild to moderate intensity PA can be performed.

The role of the qualified exercise professional in screening and programming

Most metabolic diseases are predominantly chronic diseases secondary to adverse health behaviours (i.e., sedentarism). Prediabetes, the metabolic syndrome, and type 2 diabetes can all be prevented and treated with increased PA.

Fig. 2. (A) Prediabetes physical activity (PA) clearance algorythm. Patients who have been diagnosed with having prediabetes would follow this risk algorithm for exercise clearance. Low-risk individuals would be cleared for all forms of PA, while moderate risk individuals would be cleared for light to moderate intensity activities. High-risk individuals would be recommended to seek further medical clearance for PA participation. (B) Type 2 diabetes PA clearance algorythm. Patients who have been diagnosed with having type 2 diabetes would follow this risk algorithm for exercise clearance. Low-risk individuals would be cleared for all forms of PA, while moderate-risk individuals would be cleared for light- to moderate-intensity activities. High-risk individuals would be recommended to seek further medical clearance for PA participation. (C) Type 1 diabetes PA clearance algorythm. Patients who have been diagnosed with having type 1 diabetes would follow this risk algorithm for exercise clearance. Low-risk individuals would be cleared for all forms of PA, while moderate-risk individuals would be cleared for light- to moderate-intensity activities. High-risk individuals would be recommended to seek further medical clearance for PA participation.

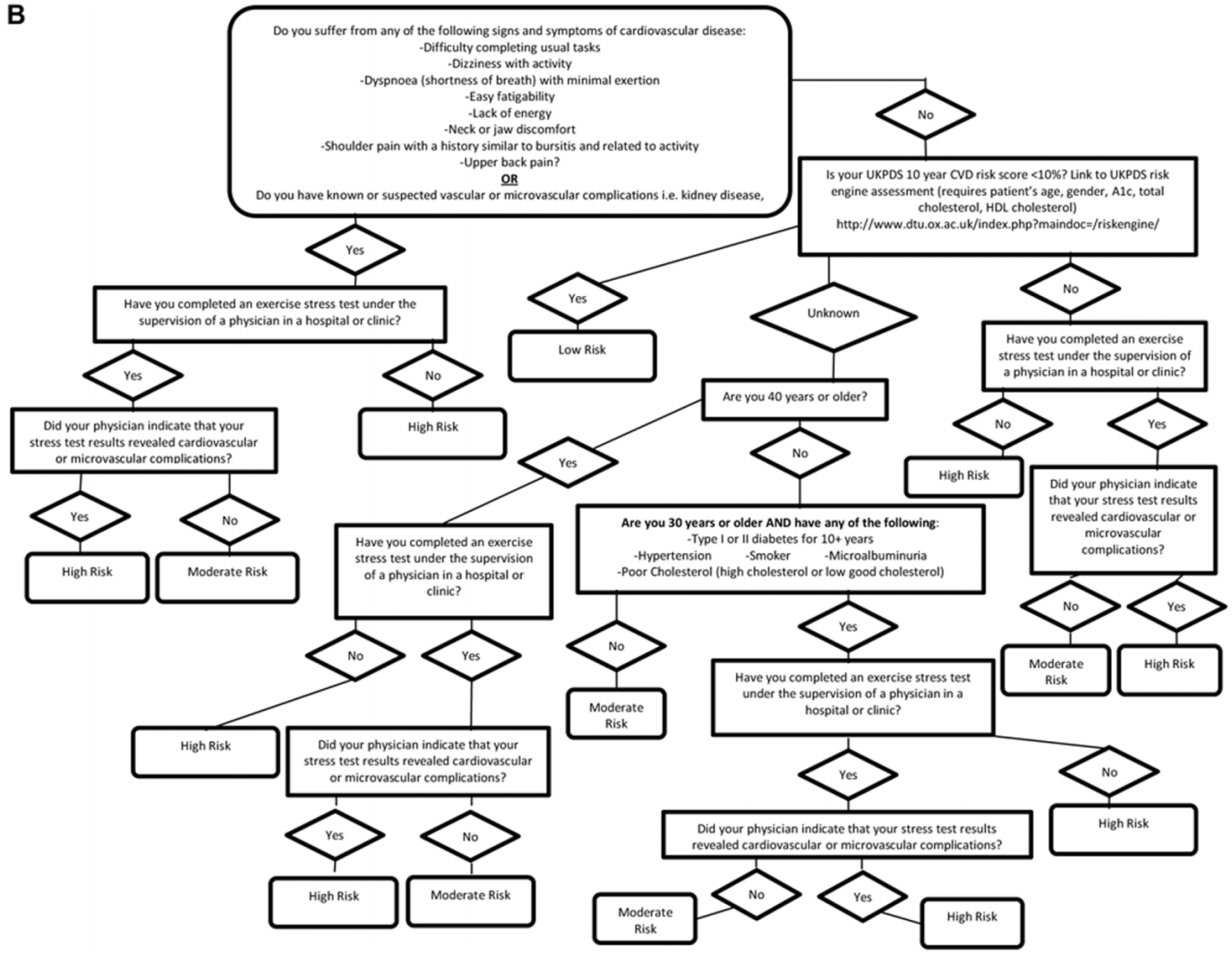


Traditionally, the health care team, which may consist of general practitioners, specialists, nurse educators, and nutritionists, works with patients who have metabolic disease to improve their condition. This treatment may or may not focus on health behavior interventions. It is time for the role of the QEP to be clarified in this health care team approach.

Despite a strong body of evidence supporting the health benefits of health behavior interventions and lifestyle modification in people with type 2 diabetes, application in medical care settings remains a challenge (Harris et al. 2003). Health care professionals, including QEPs can heighten awareness of the importance of PA participation by promoting regular exercise as a key component of therapy and identifying resources in the community that persons with diabetes might have access to (Harris et al. 2003). Structured PA counselling by a physician (Harris et al. 2003) or skilled health personnel and case managers (Kirk et al. 2004) has been effective in increasing PA participation in persons with type 2 diabetes. This intervention improves glycemic control, reduces the need for oral hypoglycemic agents and insulin, and produces modest but sustained weight loss. With appropriate advanced education in metabolic disease risks and treatments, and with an improved standard of care on exercise and metabolic disease, QEPs may be best qualified to work with individuals on exercise screening, programming, and evaluation of fitness-related outcomes.

Since about a third of the persons with type 2 diabetes are undiagnosed (Young and Mustard 2001) and because these persons also have a high risk of existing cardiovascular disease (Coutinho et al. 1999), QEPs need to be aware of the

Fig. 2 (*continued*).



typical and atypical symptoms of both diabetes and cardiovascular disease while working with clients in any setting, including fitness centers and community centers. New and current QEPs should also be required to complete advanced training modules that need to be developed based on the available clinical practice guidelines published on exercise and diabetes.

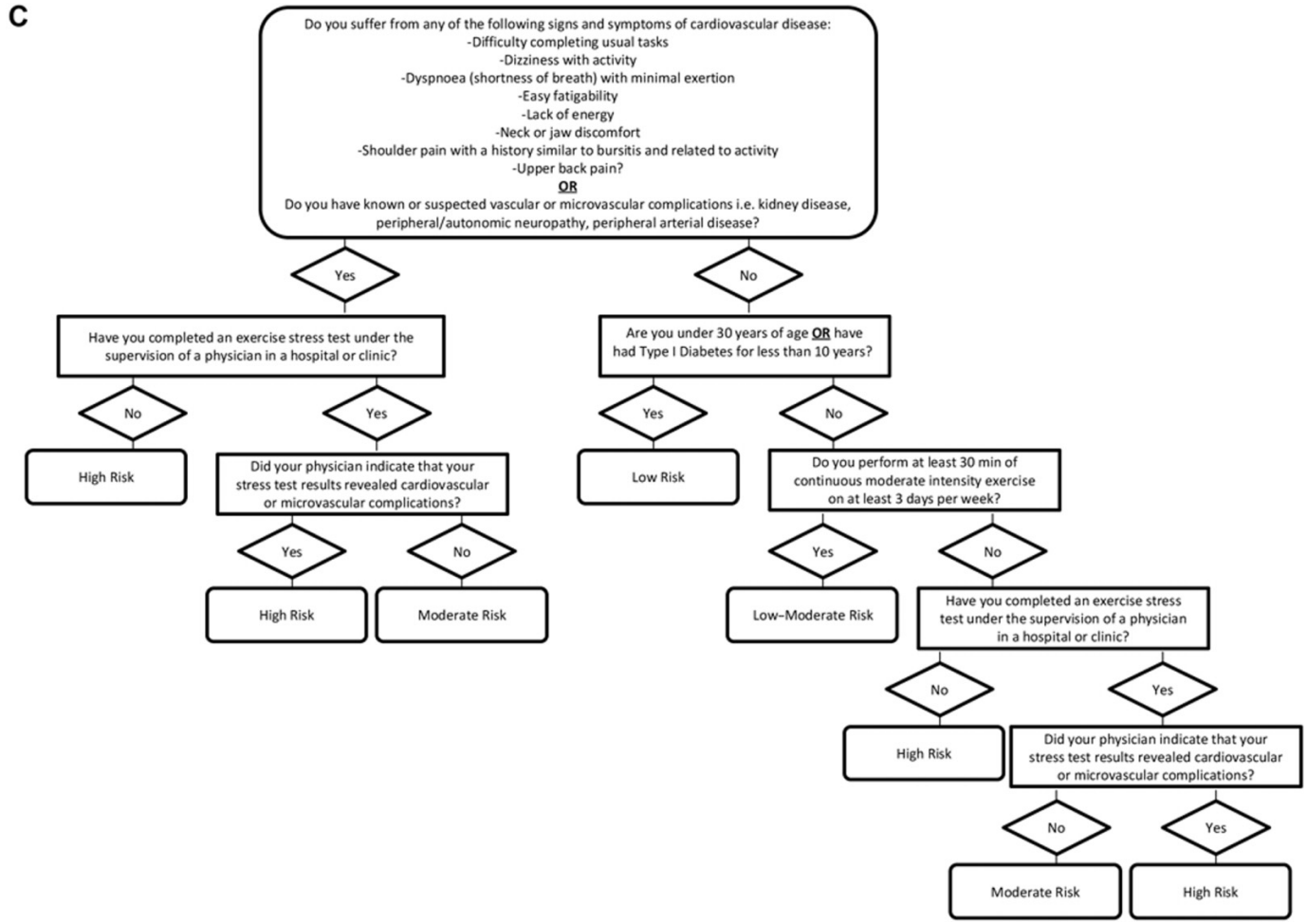
Recommendation no. 13: Qualified exercise professionals should have advanced training modules on exercise and diabetes mellitus based on the currently available position stands, clinical practice guidelines, and technical reviews published by various professional organizations (CSEP, ACSM, ADA, CDA, and AHA) (Level 4, Grade C).

Appropriateness of PAR-Q and PARmed-X for exercise screening in individuals with a metabolic disease–condition

The current PAR-Q and PARmed-X forms (revised last in 2002) have good utility for exercise screening for apparently healthy individuals and individuals with symptoms of disease and (or) a disease diagnosis. However, these forms do not clearly identify persons with diabetes or with diabetes-related complications that appear to place them at risk for an adverse event caused by vigorous exercise. The identification of a diabetes diagnosis is not explicit in 1 of the 7 screening questions, although persons with diabetes may answer "yes" to question 1 (Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?) if they have been told that they are at elevated risk for CVD events because of a diabetes diagnosis, or question 7 (Do you know of *any other reason* why you should not do physical activity?) if they think that diabetes might be a contraindication to exercise. Based on our evidence-based review, the identification of a diabetes mellitus, type 1 or 2, should be explicit on the revised PAR-Q such that these individuals can be classified as high risk for CVD related events. The question could be posed as "have you been diagnosed with either 'pre-diabetes' or 'diabetes'? If you have been diagnosed with diabetes, what type of diabetes do you have and how long has it been since your diagnosis?"

If a client has indicated that they have been diagnosed with diabetes (either type 1 or type 2), these individuals should be instructed to proceed to the next stage of screening and risk stratification (Fig. 2) and should be made aware that certain

Fig. 2 (*concluded*).



considerations and precautions are needed prior to the onset of exercise more vigorous than brisk walking (i.e., PARmed-X screening).

The PARmed-X form also does not explicitly identify diabetes as a CVD risk factor or that the diagnosis of diabetes places the client at an elevated risk for an adverse event associated with some forms of exercise. This screening process should be changed such that a patient's history of diabetes, age, and current HbA1c is considered along with their estimated CVD event risk according to either the UKPDS risk engine (those with type 2 diabetes) or with other signs and (or) symptoms of complications from diabetes.

We found no additional absolute contraindications to exercise related to metabolic disease other than what is currently stated on the current PARmed-X form (those related to severe cardiovascular disease). For persons with diagnosed diabetes, increased PA should be recommend; however, those with long standing disease, those with type 2 diabetes who have a >10% risk of a cardiovascular event based on the UKPDS risk engine, and those with diabetes-related complications (i.e., micro- and macrovascular disease) that include CVD, retinopathy, autonomic neuropathy, nephropathy, and diabetic foot ulceration may require clinical screening and possibly an exercise stress test prior to PA participation that is more strenuous than walking. For individuals who might have other comorbidities, the reader is encouraged to review the other related documents in this series (Chilibeck et al. 2011; Eves et al. 2011; Goodman et al. 2011; Jones 2011; Rhodes et al. 2011; Thomas et al. 2011).

Risk stratification and decision tree flow chart

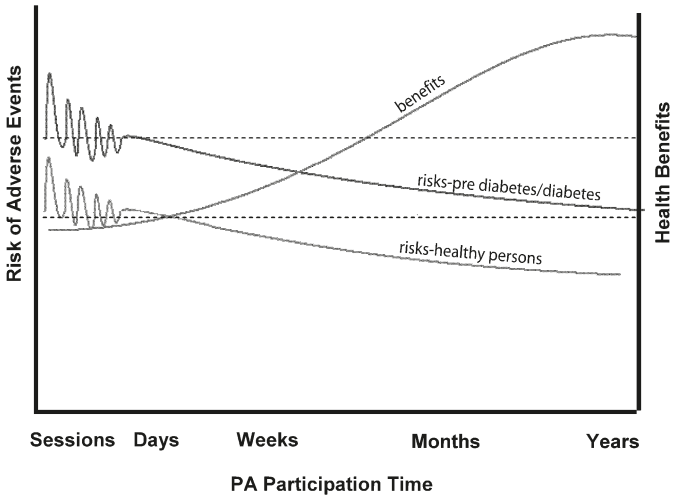
Based on the above considerations of risks and adverse events in persons with metabolic disease, we provide a new step-by-step flow chart utilizing health risk stratification that will help QEPs to appropriately screen individuals through an interview process and cardiometabolic risk assessment (Fig. 2).

Areas of investigation requiring further research

Although a considerable body of literature exists on the role of PA in promoting and maintaining metabolic health, a number of important questions related to the benefits and risks of exercise with regard to common metabolic conditions remain unanswered and require additional research. These include the following:

1. A standardized risk assessment protocol should be developed and used for all RCTs and clinical trials that use exercise and (or) PA as an intervention. This risk-assessment protocol should include documentation of all expected potentially serious adverse events (cardiac complications, MI, sudden death, retinal hemorrhage, severe

Fig. 3. Theoretical summary of relative risks for adverse events and health benefits of regular physical activity (PA) participation in persons with pre-diabetes, type 1 diabetes or type 2 diabetes and in healthy age-matched controls. Persons with a metabolic condition, such as prediabetes or diabetes, have elevated baseline risk for cardiovascular disease and other comorbidities that elevates their risks for an adverse event associated with increased PA. The level of increased risk depends on a number of factors, including age, duration of diabetes, ethnicity, history of glycemic control, and if any other risk factors are present (see also Fig. 1). These factors also likely increase the risk for an adverse event triggered by PA, particularly if the activity is of a vigorous intensity (≥6 METs). The elevation in risk for an adverse event caused by increased PA appears greatest during and in the few hours after the completion of the increase in PA. With time, however, as with normal individuals, the relative risk for an adverse event associated with increased PA may decrease to below their original baseline risk. It is also important to note that if, rather than beginning a program of increased PA, these same individuals with elevated baseline risk were to remain sedentary, their baseline risk for diabetes-related complications, including cardiovascular disease, would increase with time. After the initial period of adaptation, the health benefits outweigh any elevated risk associated with the start of a new PA program.



hypoglycemia requiring assistance from another person or medical assistance, etc.) as well as those adverse events that should be considered less serious (i.e., musculoskeletal injury and soreness).

2. Additional research evaluating dose-response patterns of exercise in preventing diabetes and cardiovascular outcomes in diabetes is urgently needed, as is a standardized protocol that examines potential adverse events (musculoskeletal, cardiovascular, metabolic, micro- and macrovascular complications) associated with differing intensities of exercise. This research is critical to develop the best and safest exercise regimes for these individuals at high risk for metabolic, microvascular, and cardiovascular complications. In particular, with the increased attention on "sprinting" as an effective exercise modality to improve cardiovascular fitness, muscle metabolism, and whole-body insulin sensitivity, a risk to benefit assessment of this particular exercise modality is urgently needed for this target population (i.e., prediabetes and type 2 diabetes).
3. More RCTs are needed to examine the benefits and safety of regular exercise on treating type 1 and type 2 diabetes in children and young adults with these diseases (in terms of metabolic and cardiovascular health). A standardized protocol that examines potential adverse events (musculoskeletal, cardiovascular, metabolic, microvascular, and macrovascular complications) is required. Finally, the question of whether patients with long-standing type 1 diabetes require medical screening prior to the initiation of vigorous exercise, needs to be investigated.

Summary and conclusions

Individuals with prediabetes and diabetes (type 1 and type 2) have higher baseline risk for cardiovascular disease and other macro- and micro-vascular complications. As such, persons with prediabetes, type 1 diabetes and type 2 diabetes with or without co-morbidities require special screening prior to the initiation of increased PA participation or a new exercise program. For some of these individuals, the relative risk of an adverse event associated with increased PA (particularly with vigorous activities) is elevated, at least during the initial period after the onset of a new PA regimen. With increased PA participation, however, much of the adverse event risk decreases, particularly for cardiovascular complications, as do the risks for the development of many other diabetes-related complications (Fig. 3). To assist with the initial evaluation of these individuals, we provide a new evidence-based pre-exercise screening process that should be used for these individuals in health clubs, recreation centers and other places where PA programming and participation is being offered. In addition, this process will be of value to all health care providers, including QEPs, who recommend PA participation for people with cardiometabolic disease.

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Appendix A

Appendix A appears on the following pages.

Table A1. Metabolic search strategy — keywords, search statements, boolean logic, and results from various databases searched.

Search no.	Keywords	Medline	CINAHL	EMBASE (wk 14, 2008)	Cochrane, etc.
1	Diabet*.mp	291 737	37 910	259 225	17 003
2	(mellitus or non insulin or non-insulin or noninsulin or type 2 or type II or type-2 or type-II or adult onset or adult-onset or late onset or late-onset or maturity onset or maturity-onset or slow onset or slow-onset or NIDDM or NID DM or mody).mp	358 782	31 133	291 048	14 672
3	(type 1 or type I or lipoatrophic or diabet* ketoacidosis or hyperglycemia or glucose intolerance or hyperinsulin* or insulin resistan*).mp	275 154	10 514	208 822	10 539
4	(metabolic syndrome* x or dysmetabolic syndrome* x or insulin resistan* syndrome x or metabolic cardiovascular syndrome* or (cardiovascular syndrome* adj5 metabolic) or (syndrome* adj5 metabolic cardiovascular) or metabolic x syndrome* or (syndrome* adj5 metabolic x) or (x syndrome* adj5 metabolic) or reaven syndrome* x or (syndrome* x adj5 reaven) or (syndrome* x adj5 insulin resistan*) or (syndrome* x adj5 metabolic*)).mp	6 634	1 509	9 707	224
5	(Obes* or weight* or fat or adipos* or BMI or body mass index or waist-hip ratio or waist hip ratio or fat distribut* or overnutrition).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	867 213	63 313	625 442	46 129
6	((((((((((Exercise* or movement or exert* or muscle contract* or isometric contract* or isotonic contract* or muscle*) adj5 stretch*) or weight*) adj3 train*) or circuit*) adj3 train*) or weight*) adj3 lift*) or athlet*) adj3 train*) or aerobic* or fitness* or sport* or physical educat* or physical* fit* or physical train* or motor activit* or sport* or athletic* or endurance) adj3 train*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	18 100	6 135	14 747	3 021
7	(locomot* or danc* or tai ji or tai chi or walk* or yoga or runn* or jogg* or swim* or gymnastic*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	124 183	18 537	107 176	8 355
8	(((((Risk* or risk-assess* or benefit-risk* or risk-benefit* or adverse effect* or case-mix adjustment* or severity-of*adj3 measure* or predict*) adj3 injur*) or predict*) adj3 death) or outcome* or safe* or risk-evaluat* or rehabilit* or harm).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	1 036 271	212 435	1 000 511	139 051
9	(((((logistic adj1 model*) or logistic) adj1 regression*) or logit) adj1 model*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	15 343	3 156	11 077	2 504
10	(liver or liver failure or hepatic failure, or (hepat* adj5 failure)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	11 383	3 760	10 155	653
11	(kidney failure or (kidney adj 3 failure) or renal failure or (renal adj3 failure)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	67 250	8 202	498 423	12 775
12	1 or 2 or 3 or 4 or 5 or 11 or 12	109 720	7 157	95 396	5 455
13	6 or 7 or 9	2 029 302	112 339	1 672 531	78 351
14	13 and 14	14 6872	26 376	128 353	11 903
15	8 and 15	25 806	6 124	7 898	3 229
16	(randomized controlled trial or RCT or Random* control* trial or crossover trial).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	3 147	1 479	93 376	1 474
17	16 and 17	254 221	7 248	156 200	40 485
18	(cohort study or cohort or cross sectional or observational or observation*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	507	75	11 722	524
19	16 and 19	633261	61 002	475 021	30 034

Table A1 (*concluded*).

Search no.	Keywords	Medline	CINAHL	EMBASE (wk 14, 2008)	Cochrane, etc.
20	(Review* or meta analys* or metanalys* or metaanalys* or pooled or effective* or evaluat* or evidence* or efficac* or outcome* or impact* or guideline* or best practic* or best-practic* or best practis* or best-practis*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]	439 4 517 997 2 709	196 397 159 1 249	10 372 3 830 787 12 487	428 290 714 1 411
Sport Discuss	((Obes* or weight* or fat or adipos* or BMI or body mass index or liver failure or hepatic failure, or kidney failure or renal failure) or (Diabet* and (mellitus or non insulin or non-insulin or noninsulin or type 2 or type II or type-2 or type-II or adult onset or adult-onset or late onset or late-onset or maturity onset or slow onset or slow-onset or NIDDM or NID DM)) and (Exercise* or isometric contract* or isotonic contract* or weight train* or circuit* train* or sport* or physical* fit* or athletic*) and (Risk* or adverse effect* or death))				1 122
1	diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/ or diabetes mellitus, lipoatrophic/ or diabetic ketoacidosis/ or hyperglycemia/ or glucose intolerance/ or hyperinsulinism/ or insulin resistance/ or metabolic syndrome x/	181 978			
2	overnutrition/ or obesity/ or obesity, morbid/	81 815			
3	body weight/ or overweight/	133 920			
4	body fat distribution/ or adiposity/ or body mass index/ or body size/ or body weight/ or overweight/ or waist-hip ratio/	169 051			
5	exertion/ or exercise/ or movement/ or locomotion/ or running/ or jogging/ or swimming/ or walking/ or dependent ambulation/ or motor activity/ or muscle contraction/	274 340			
6	isometric contraction/ or isotonic contraction/	10 162			
7	weight lifting/	2 924			
8	exercise movement techniques/ or dance therapy/ or exercise/ or exercise therapy/ or muscle stretching exercises/ or tai ji/ or walking/ or yoga/	66 432			
9	"physical education and training"/ or gymnastics/	11 077			
10	physical endurance/ or anaerobic threshold/ or exercise tolerance/	15 343			
11	Risk/	76 054			
12	1 or 2 or 3 or 4	383 258			
13	5 or 6 or 7 or 8 or 9 or 10	307 967			
14	12 and 13	22 606			
15	11 and 14	366			
16	(clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "review" or twin study or validation studies)	544			
17	15 and 16	0			
18	Cohort Study/ or Closed Cohort Study/ or Incidence Study/ or Cohort Analysis/ or Prevalence Study/ or Cross Sectional Analyses/ or Cross-Sectional Analysis/ or Cross Sectional Study/	160 878			
19	15 and 18	33			
20	("article reviews (acp journal club)" or "article reviews (dare)" or evidence based medicine reviews or "topic reviews (cochrane)")	157			
21	15 and 20	0			

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Appendix B

Standard risk factors associated with coronary artery disease

1. Hypertension
   - High blood pressure confirmed by measurement on at least 2 separate occasions
     - Systolic blood pressure: 140 mm Hg or greater
     - Diastolic blood pressure: 90 mm Hg or greater
   - Using antihypertensive medication
2. Hypercholesterolemia
   - Low-density lipoprotein: > 130 mg·dL^{-1} (3.4 mmol·L^{-1})
     - If low-density lipoprotein is not available, use total cholestol criteria instead:
     - Total serum cholesterol: >200 mg·dL^{-1} (5.2 mmol·L^{-1})
   - High-density lipoprotein (HDL) cholesterol: <40 mg·dL^{-1} (1.03 mmol·L^{-1})
   - Using lipid-lowering medication
3. High serum HDL cholesterol (negative risk factor)
   - >60 mg·dL^{-1} (1.6 mmol·L^{-1})
     - High serum HDL cholesterol decreases the risk of coronary artery desease
     - Subtracts 1 risk factor from sum of positive risk factors above
4. Impaired fasting glucose
   - Fasting blood glucose: 100 mg·dL^{-1} (5.6 mmol·L^{-1}) or greater confirmed by measurements on at least 2 separate occasions
5. Obesity
   - Exercise professional should use clinical judgment when evaluating this risk factor
   - Professional opinions vary regarding the most appropriate markers and thresholds for obesity
     - Body mass index of 30 kg·m^{-2} or greater
     - Waist/hip ratio greater than 0.95 (men) and 0.86 (women)
     - Waist girth greater than 102 cm (men) and 88 cm (women)
6. Sedentary lifestyle
   - Not participating in a regular exercise program
   - Not accumulating 30 min or more of moderate physical activity on most days of the week
7. Smoking
   - Current cigarette smoker
   - Quit within previous 6 months
8. Family history
   - Myocardial infarction, coronary revascularization, or sudden death
     - Before 55 years of age in father or other male first degree relative (i.e., brother or son)
     - Before 65 years of age in mother or other female first degree relative (i.e., sister or daughter)

The ACSM recommends medical screening and an exercise tress test for anyone over the age of 40 years with any of the above 8 risk factors.

Appendix C

Table C1. Potential cardiometabolic and musculoskeletal risks of exercise in persons with prediabetes and diabetes.

Cardiovascular
Cardiac dysfunction and arrhythmias due to ischemic heart disease (often silent)
Excessive increments in blood pressure during exercise
Postexercise hypotension
Microvascular
Retinal hemorrhage
Increased proteinuria
Acceleration of microvascular disease
Metabolic
Worsening of hyperglycemia and ketosis
Hypoglycemia in patients taking insulin or oral hypoglycemic agents
Musculoskeletal
Musculoskeletal soreness and injury
Foot ulcers (particularly in presence of neuropathy)
Orthopedic injury related to neuropathy

Note: Adapted from the American Diabetes Association (Sigal et al. 2004) and the American College of Sports Medicine (Albright et al. 2000).

Appendix D

Table D1. Relative and absolute contraindications to exercise.

Absolute contraindications
Recent and significant change in resting ECG that has not been adequately investigated and managed
Unstable angina pectoris
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
Uncontrolled symptomatic heart failure
Severe symptomatic aortic stenosis
Suspected or known dissecting aneurysm
Acute myocarditis or pericarditis
Acute thrombophelbitis or intracardiac thrombi
Acute pulmonary embolus or pulmonary infarction
Untreated high-risk proliferative retinopathy
Recent significant retinal hemorrhage
Acute or inadequately controlled renal failure
Acute infections
Relative contraindications
Fasting blood glucose>300 mg·dL^{-1} or >250 mg·dL^{-1} with urinary ketone bodies
Uncontrolled hypertension with resting systolic blood pressure>200 mm Hg or diastolic blood pressure>110 mm Hg
Severe autonomic neuropathy with exertional hypertension
Moderate stenotic valvular heart disease
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Tachyarrhythmias or bradyarrhythmias
High-degree atrioventricular block
Ventricular aneurysm
Electrolyte abnormalities (e.g.hypokalemia, hypomagnesemia)
Uncontrolled metabolic disease (etoxicosis, myxedemia)
Chronic infectious disease (e.g., hepatitis, AIDS)
Neuromuscular, musculoskeletal or rheumatoid disorders that are exacerbated by exercise
Complicated pregnancy

Note: Adapted From Gordon (2002).

Appendix E

Table E1. Large scale prospective cohort studies of "lifestyle" intervention to prevent diabetes from a state of prediabetes.

Trial	Delivery and goals	Exercise	Risk reduction
Malmo study (Eriksson and Lindgärde 1991)	1:1 counselling	Underwent 6 mo of supervised physical training and 6 mo of dietary treatment in a randomized crossover design	50%
N = 181 subjects with IGT, aged 47–49 y in Malmö, Sweden	Exercise and diet		
Da Qing IGT and Diabetes Study (Pan et al. 1997)	1:1 Counseling (5 contacts per y)	Daily aerobic (+100 min/week walking)	31% diet group
N = 577 subjects with IGT	Exercise vs. diet vs. exercise plus diet		46% exercise group
	Low cal (2200 kcal)		42% diet and exercise
	Low fat (25%–30% fat)		
Finnish Prevention Study (Tuomilehto et al. 2001)	1:1 counseling exercise and diet 5% wt. Loss	30 min·d^{-1} moderate exercise	58%
N = 522 overweight/obese subjects with IGT	Low cal (1523 kcal)	Structured circut training	
	Low fat (25%–30% fat)		
	High fiber (15 g/100kcal)		
Indian Diabetes Prevention Study (Ramachandran et al. 2006)	1:1 counciling exercise and diet	Subjects given advice on lifestyle modification	28%
N = 531 men and womens with IGT	Metformin	Metformin	26%
	Metformin plus lifestyle	Metformin plus lifestle	28%
Diabetes Prevention Program (Knowler et al. 2002)	1:1 counseling 7% weight loss	150 min·wk^{-1} walk	58%
3234 American adults with glucose intolerance (elevated fasting and IGT)	Low calorie (decrease by 450 kcal)	Metformin	31%
	Low fat (<25%)		

Appendix F

Other exercise screening guidelines

(1) The Canadian Diabetes Association (CDA)'s 2008 Clinical Practice Guidelines on exercise screening (Sigal et al. 2008)

According to the 2008 CDA's Clinical Practice Guidelines, persons with diabetes require special consideration before starting an exercise regimen. Although the benefits of increased PA outweighs the risk for most individuals, they state that "An exercise ECG stress test should be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to undertake exercise more vigorous than brisk walking [Grade D, Consensus]." No mechanism is provided to evaluate CVD risk, however.

(2) American College of Sports Medicine (ACSM)'s recommendations on exercise screening for diabetes

Initially, ACSM advised that anyone over the age of 35 years who planned to start an exercise program should have a complete medical examination, including an electrocardiogram (ECG). Moreover, the ACSM proposed that people over the age of 35 years who had certain risk factors for heart disease, including a family history of heart disease, a history of heavy smoking, high blood pressure, and high lipid levels, should undergo clinical screening and an exercise evaluation. The purpose of this recommendation was to identify all those who have heart disease that may be at high risk of having a cardiac event or sudden cardiac death.

Note that for asymptomatic individuals (i.e., those who have not been diagnosed with a medical condition), the ACSM and the American Heart Association (AHA) suggest pre-exercise noninvasive exercise testing in the presence of 2 or more coronary risk factors or in patients >40 years of age with only 1 risk factor. As diabetes is a risk factor for coronary heart disease, according to these recommendations, all persons with diabetes over the age of 40 would need an exercise stress test before initiating an exercise program.

(3) American Diabetes Association (ADA)'s recommendations for diabetes mellitus and exercise (2002)

For persons with diabetes mellitus, the ADA suggests that a graded exercise test may be helpful if a patient is about to embark on a moderate- to high-intensity exercise program if they are aged >35 years or if they have type 2 diabetes >10 years' duration or if they have had type 1 diabetes of >15 years duration. In addition, this recommendation for a graded exercise evaluation is extended to those who are younger or who may have had diabetes duration of less than that mentioned above, but have the presence of any additional risk factors for CAD, or if they have any presence of microvascular disease (proliferative retinopathy or nephropathy including microalbumin), or if they have peripheral vascular disease, or autonomic neuropathy.

(4) The American College of Cardiology–American Heart Association recommendations for exercise and diabetes

The above organizations recommend the use of medical screening with exercise ECG testing among patients with diabetes mellitus and the following conditions BEFORE they engage in moderate to vigorous activity:

1. Known or suspected CAD
2. T1DM for >15 years
3. T2DM for >10 years or age ≥35 years
4. Additional atherosclerotic risk factors
5. Evidence of microvascular disease, PAD, or autonomic neuropathy (www.acc.org/clinical/guidelines/exercise/dirIndex.htm)

(5) The US Preventive Services Task Force

The USPSTF concluded that there was insufficient evidence to recommend for or against screening for CAD in asymptomatic persons with diabetes mellitus, including before they begin an exercise program.