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Variability in Individual Response to Aerobic Exercise Interventions Among Older Adults

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Abstract

Although a plethora of evidence supports the benefits of exercise among older adults, a majority of studies have emphasized group differences, while giving little, if any, attention to individual differences. Given the lack of data on variability in response, the present review examined how nonresponse to aerobic exercise has been defined in older adult populations and characteristics associated with nonresponse among older adults. The results of this review suggest that inter-individual variability in response of maximal oxygen consumption to aerobic exercise interventions is prevalent among older adults (1.4–63.4%); age, sex, race, and BMI may not be critical determinants of nonresponse; whereas health status, baseline fitness, and exercise dose appear important. Future intervention studies should evaluate and report the variability in individual response of older adults to exercise; investigators should develop programs that allow for modification of components to assist older adults in achieving optimal benefit from exercise programs.

Keywords

aerobic exercise; heterogeneity; responsiveness; nonresponse; aging

Background

There is a plethora of evidence supporting the benefits of increasing exercise and reducing sedentary time among individuals of many different ages and fitness levels (Garber et al., 2011; Stamatakis, Hamer, & Dunstan, 2011). Work with older adults demonstrates the positive influence of exercise on cardiovascular morbidity and mortality, cancer, and a range of other health conditions (Nelson et al., 2007). However, despite evidence supporting the benefits of aerobic exercise, a vast majority of published studies have focused on main effects and group differences, while giving little, if any attention, to individual differences. Thus, most conclusions related to the magnitude of the effects of exercise interventions on study outcomes are based on mean changes observed across groups, and may not be representative of the potential benefit, harm, or neutral effect for an individual.

Many different terms have been used to describe this phenomenon, including poor response, nonresponse, and negative response to exercise interventions. The most common definition used is a lack of change of an outcome of interest in the expected direction (Bouchard & Rankinen, 2001; Bouchard, 1995; Bouchard et al., 2012; Scharhag-Rosenberger, Walitzek, Kindermann, & Meyer, 2012). Nonresponse has been simply described as the absolute change or percent change in the variable of interest. A more complex definition includes the relative distribution of change observed in a control group who did not receive the study intervention (Leifer et al., 2014). However, the rationale for the definition of nonresponse used in a given study is frequently not described.

Describing response variability or “nonresponse” is also dependent on clearly defining the outcome of interest. For example, in an aerobic training study, the primary outcome may be aerobic fitness measured via maximal cardiopulmonary exercise test, or aerobic function measured via timed walking test. The selection of this primary outcome variable has significant implications. Thus, it is essential thoughtful decisions are made when selecting the specific outcome of interest and when defining what constitutes nonresponse or negative response for a given study.

There has been some work to evaluate the extent of variability in response to exercise interventions, although almost exclusively with younger populations. This is likely due to the potential bias and complication introduced by inclusion of older adults with multiple chronic conditions which could influence response to the intervention in unanticipated or negative ways. Studies in healthy individuals and young adults indicate substantial inter-individual variability in physiological responses to structured exercise. Although it is generally accepted that 3–4 months of regular endurance training in which the participant is adherent to the prescribed exercise results in improvements of 10–25% in maximal aerobic power (Bouchard, 1995), it is often overlooked that these values represent mean differences that will not be achieved by most individuals. Rather, the actual percent change for an individual may be 0%, 100%, or greater, depending on genetic contributions, training program, and baseline fitness. The rates of nonresponse in peak VO_2 , which was defined as failure to demonstrate an improvement of greater than twice the “typical error rate” of VO_2 peak (Gurd et al., 2016) and an improvement of less than two standard deviations from the mean (T. P. Higgins, Baker, Evans, Adams, & Cobbold, 2015) reported in two recent studies of young adults were 17% and 19%, respectively, indicating that although there were overall improvements in oxygen consumption among individuals who received aerobic exercise training in both studies, there was substantial variation in response.

Prevalence of nonresponse to aerobic exercise has also been examined in young and middle age adults with respect to glucose homeostasis. A recent review suggested that nonresponse (defined in this review as no improvement in glucose hemostasis as measured using an oral glucose tolerance test) was quite prevalent, ranging from 7% to 63% in the included studies (Böhm, Weigert, Staiger, & Häring, 2015). The results of this review suggest substantial variability in response to treadmill and cycle-based aerobic exercise among young and middle age adults, but the causes of nonresponse are largely unknown.

Although several studies have examined predictors of successful response to exercise interventions, this work has also been primarily in young adults. At least one review evaluating differential responses in blood pressure, triglycerides, and high density lipoprotein cholesterol that suggested that women have an attenuated response to exercise training as compared to men (Wilmore, 2001). Hypothesized reasons for nonresponse include insufficient training stimulus (i.e., intensity), gender-related differences in cardiorespiratory response to exercise, and baseline fitness (Earnest, Blair, & Church, 2010; Kohrt et al., 1991). However very little has been done to evaluate these contributors among older adults, which has significant implications for exercise research.

When conclusions are drawn on the basis of mean exercise training responses, information that could optimize exercise training programs may be lost (Bouchard & Rankinen, 2001). This could be particularly relevant for older adults, given the increased heterogeneity among older adults with respect to health, physical function, work and leisure activities, and social environment (Lowsky, Olshansky, Bhattacharya, & Goldman, 2014). This is supported by limited evidence from resistance training studies, which suggests that variation in training adaptations may be greater among older adults than younger adults (Newton et al., 2002). The reporting of mean differences, although rooted in inferential statistics and providing the opportunity for consideration of the generalizability of study findings, is likely to conceal a wide range in potential responses. For example, despite a high level of participation in aerobic exercise for several months, responses may range from a decrease in aerobic capacity, to a doubling of aerobic capacity under similar training protocols (Bouchard, 1995). Given that exercise training is frequently used for disease prevention, risk factor reduction, and prevention of age-related decline in physical performance, attention should be directed toward the acknowledgment and assessment of individual differences in training responses (Karavirta et al., 2011).

According to a position statement of the American College of Sports Medicine on prescribing exercise for healthy adults, trainability of VO_2 max is not reduced by age (Garber et al., 2011). In this position statement, the authors recognize that the magnitude of effect of a particular exercise training regimen can vary substantially among individuals, and “there are some exercisers who may not respond as expected” (p. 1345). Multiple factors are associated with variation in exercise training effects between individuals, including the characteristics of the training regimen, environmental conditions, and numerous individual factors, such as habitual physical activity, fitness level, physiological and genetic variability, and social and psychological factors. Although age and sex appear to have relatively little to do with exercise training response, this is not universally reported (Marcus et al., 2006). Inter-individual variability is an understudied aspect of health research that could provide additional, complementary information to average values from a population. Thus, further work is needed to evaluate the prevalence of nonresponse to exercise interventions among older adults and the potential role of health status, baseline function, and other individual and intervention characteristics in nonresponse to aerobic exercise.

Review Questions

Given the lack of data on variability in response to aerobic exercise among older adults, there is a need to synthesize the existing literature to inform the direction and focus of future research priorities. Therefore, the aim of the present review was to address the following research questions: 1) How has nonresponse been defined and measured in older adult populations?, 2) What is the extent of inter-individual variability in response to aerobic exercise interventions among older adults?, 3) What participant and study characteristics are associated with inter-individual variability?, and 4) What hypotheses have been made with respect to why some older adults do not respond equally to exercise interventions?

Method

Search Strategy

Literature searches were performed using OVID MEDLINE (including the OVID MEDLINE In-Process database), EMBASE, and CINAHL. Articles related to variability in response, poor response, or lack of response to aerobic exercise interventions in older adults were retrieved. Given the lack of a specific subject heading describing the phenomenon of nonresponse, trainability, or variability in response, a complex search strategy was employed to identify relevant articles. The subject heading “exercise” was used in combination with a variety of terms to describe the variability in response (e.g., “differential”, “inadequate”, “insufficient”), which were selected based on terms present in the literature. Additional limits were placed on the searches to restrict the output to articles in English and those that included a middle aged or older (45 years and older) population (except for OVID MEDLINE – In Process, in which age limits were unavailable). Age 45 years and older was used as the age limiter at this stage of the search as the database available limiters were “middle age (45 to 64 years)” and “all aged (65 and over)” and we wanted to ensure no potentially eligible articles were inadvertently excluded. No limits were placed on publication date, thus the search included articles published between January 1, 1946 and May 1, 2017. A sample search strategy used for the OVID MEDLINE search is reported in Table 1. Similar strategies were used for the OVID MEDLINE - In Process, EMBASE, and CINAHL databases. Searches of PROSPERO and the Cochrane Database were also conducted to determine if protocols for related systematic reviews had already been published.

Selection of Studies

To be eligible for inclusion in this review, articles had to meet the following criteria:

- be an original report of an aerobic exercise intervention
- sample with a mean age of 55 years or older
- independently living participants
- primary component of intervention was aerobic exercise
- report nonresponse or response variability in any outcome of an intervention
- written in English

Studies meeting any of the following criteria were excluded from this review:

- inclusion of individuals <18 years of age
- nursing home population
- intervention was 6 weeks or less in length
- home, outpatient, or inpatient rehabilitation program after acute illness
- qualitative studies
- observational studies
- non-English publication
- letters to the editor, systematic reviews, or conference proceedings

As there is a lack of consensus among researchers in the field regarding the duration of exercise needed to actually capture nonresponse (versus an inadequate training stimulus), studies of less than 6 weeks in duration were excluded in order to reduce the possibility that exercise duration was too short to produce a response. Studies of interventions consisting of combination programs of aerobic plus resistance training were included, if greater than 50% of the protocol-prescribed exercise was aerobic in nature. Studies that included two or more intervention arms (such as aerobic and resistance) were included if the outcomes of the training groups were reported separately. In addition to the database searches previously described, reference lists of the selected articles were also reviewed for additional eligible articles, using the same inclusion and exclusion criteria.

Data Extraction

The following data were abstracted from each included article: study purpose, targeted outcome, characteristics of the study and study participants (type of study, guiding theory or empirical framework, sampling procedure and sample size), key components of the intervention (elements, dose, strength), method for assessing intervention fidelity, and length of follow-up period. Additional abstraction included data on the primary findings of the study, definition of nonresponse, observed prevalence of poor response or variability in response, and factors related to nonresponse or variability in response.

Determination of Methodological Quality and Strength of the Evidence

The methodological quality of the studies was assessed using Cochrane's risk of bias assessment tool (J. Higgins & Green, 2011). Consistent with recommendations of the Cochrane Collaboration, an assessment of the risk of bias was used, rather than a rating or checklist of study quality, given that studies of high quality may still have a substantial risk of bias. The strength of the evidence was determined based on an assessment of the key domains identified by the Agency for Healthcare Research and Quality, which are quality, quantity, and consistency (West et al., 2002). In addition to quality, the number of articles that reported similar factors related to poor response, their outcomes, and the consistency among the reported results were evaluated qualitatively to determine the strength of the evidence for each reported factor and related variability in response to aerobic exercise interventions. Study selection, extraction of data, and bias assessment was conducted by the

primary author and reviewed by two co-authors. When questions arose, all three authors reviewed the full text document and came to a consensus on its status.

Results

A total of 1753 articles were identified through a search of: OVID MEDLINE (n=650), OVID MEDLINE – In Process (n=595), EMBASE (n=332), and CINAHL (n=176). An additional 17 articles were identified via search of the reference lists of relevant articles. After removing duplicates, 1478 unique articles were screened for inclusion (Figure 1). Upon completion of title and abstract screening and full-text review, a total of 17 articles representing 12 unique studies with 5116 unique participants were eligible for inclusion (Chmelo et al., 2015; Church et al., 2009; Earnest et al., 2010; Fielding et al., 2007; Gardner, Parker, Montgomery, & Blevins, 2014; Kohrt et al., 1991; Lam et al., 2010; Leifer et al., 2014; Luo et al., 2017; Mentz et al., 2013; Osler et al., 2015; Pandey et al., 2015; Sisson et al., 2009; Skinner et al., 2001; Swift et al., 2016; van Gool et al., 2005; Yalamanchi et al., 2016).

Characteristics of the studies can be found in Table 2. All eligible articles reported the results of studies conducted in the US except for one article reporting the results of a Swedish study (Osler et al., 2015) and one pooling data from two similar studies conducted in the United States and Germany (Lam et al., 2010). Participant demographic characteristics varied greatly across the studies. The mean age of the sample in each included article ranged from 55.7 (standard deviation [*SD*] 4.1) years (Skinner et al., 2001) to 76.5 (*SD* 4.2) years (Fielding et al., 2007). The smallest study included 14 participants (Osler et al., 2015), while the largest included 2311 participants (Mentz et al., 2013). With respect to distribution by sex, the percent of the sample that was female varied from 25% (Mentz et al., 2013) to 100% in the articles that reported various outcomes of the Dose-Response to Exercise in post-menopausal Women (DREW) study (Church et al., 2009; Earnest et al., 2010; Sisson et al., 2009; Swift et al., 2016).

The health status of the study participants also varied substantially between the articles. While several articles included primarily healthy participants who were overweight or obese (Chmelo et al., 2015; Church et al., 2009; Earnest et al., 2010; Osler et al., 2015; Sisson et al., 2009; Swift et al., 2016), others examined the effects of exercise among individuals with heart failure (Leifer et al., 2014; Luo et al., 2017; Mentz et al., 2013), peripheral artery disease (Gardner et al., 2014), diabetes (Pandey et al., 2015; Yalamanchi et al., 2016), osteoarthritis (van Gool et al., 2005), or individuals who had a stroke (Lam et al., 2010). Interventions ranged in length from 3 months (Gardner et al., 2014; Lam et al., 2010; Leifer et al., 2014) to 2.6 years (Luo et al., 2017), and typically involved treadmill walking or stationary cycling as the primary form of exercise. In addition to the aerobic component, 4 studies evaluated the effects of a combination of aerobic and resistance training (Fielding et al., 2007; Pandey et al., 2015; van Gool et al., 2005; Yalamanchi et al., 2016). As expected, the primary outcome evaluated varied across studies, but 12 of the 17 articles included VO₂ peak (Chmelo et al., 2015; Earnest et al., 2010; Lam et al., 2010; Leifer et al., 2014; Luo et al., 2017; Mentz et al., 2013; Pandey et al., 2015; Sisson et al., 2009; Swift et al., 2016) or VO₂ max (Kohrt et al., 1991; Osler et al., 2015; Skinner et al., 2001) as either a primary or

secondary outcome. Additional relevant outcomes included disease-specific measures such as hemoglobin A1c (HbA1c) and glucose tolerance (Pandey et al., 2015), claudication (ischemic leg pain) onset time (Gardner et al., 2014), body composition (Yalamanchi et al., 2016) and weight loss (Church et al., 2009; Swift et al., 2016).

Defining and Measuring Nonresponse

Among the included articles, varying terminology was used to address the concept of variability in response to exercise, including trainability, heterogeneity of response, differential response, and insufficient response (Table 3). Of the 17 included articles, 9 provided a specific definition of nonresponse (Chmelo et al., 2015; Church et al., 2009; Gardner et al., 2014; Leifer et al., 2014; Osler et al., 2015; Pandey et al., 2015; Sisson et al., 2009; Swift et al., 2016; Yalamanchi et al., 2016). These definitions can be grouped into two broad categories: 1) definitions based on whether the absolute value of the change in the outcome of interest from baseline to follow-up is different from 0, and 2) definitions characterized by achievement (or lack of achievement) of a specific clinical or research-based benchmark. Of the studies that defined nonresponse, more than half used the first definition (Chmelo et al., 2015; Church et al., 2009; Gardner et al., 2014; Osler et al., 2015; Sisson et al., 2009; Yalamanchi et al., 2016). The authors of these articles tended to classify response based on the absolute value of the change in the outcome of interest from baseline to follow-up, with a change of 0 or undesirable change (such as a decrease in VO₂ peak from baseline to follow-up) being considered “nonresponse”. The slightly less common strategy was to define nonresponse based on the clinical significance of the change in the outcome variable from baseline to follow-up (according to accepted norms) (Pandey et al., 2015; Swift et al., 2016), or the change with respect to the normal distribution of the outcome of interest (Leifer et al., 2014).

Prevalence of Nonresponse

Overall, few studies reported the extent of the problem of nonresponse among older adults. Further, estimates of the prevalence of nonresponse varied widely based on the characteristics of the sample and targeted outcome variable(s). Less than half of the articles (n=7) reported the number of participants who did not respond or experienced a negative response to the intervention (Table 3) (Gardner et al., 2014; Kohrt et al., 1991; Leifer et al., 2014; Osler et al., 2015; Pandey et al., 2015; Sisson et al., 2009; Swift et al., 2016).

Of the studies that reported the prevalence of nonresponse, most included oxygen consumption (either VO₂ peak or VO₂ max) as an outcome variable (n=5) (Leifer et al., 2014; Pandey et al., 2015; Sisson et al., 2009; Skinner et al., 2001; Swift et al., 2016). Among these studies, estimates of nonresponse in oxygen consumption to aerobic or a combination of aerobic and resistance exercise varied from 1.4% (Skinner et al., 2001) to 63.4% (Pandey et al., 2015), possibly related to differences in exercise program and delivery. An even greater degree of nonresponse was observed in two studies that evaluated outcomes other than oxygen consumption. In a secondary analysis of the DREW study, Swift et al. (2016) reported that approximately 73% of the sample did not experience either a clinically meaningful or minimal weight loss during the study period. Gardner et al. (2014) also observed a high prevalence of nonresponse – 63% of a subsample of participants (women

with diabetes) included in their aerobic exercise study for peripheral artery disease did not experience an improvement in claudication onset time. Similarly, Chmelo et al. (2015) found that 13% (n=4) demonstrated no change or a decrease in VO₂ peak following 5 months of aerobic exercise 4 days per week. However, with respect to response in the 400-meter walk, 16% of participants did not experience improvements, while 25% did not experience improvements in usual gait speed and 28% did not improve their chair rise time. For some individuals, nonresponse was observed in multiple outcomes, 2 of the 4 individuals who did not have an improvement in VO₂ peak were also nonresponsive in at least one other functional measure. Thus, there is variability in the prevalence of nonresponse observed among older adults in the included publications.

Factors Associated with Nonresponse or Variability in Response

Of the 17 included articles, a wide variety of participant and intervention characteristics were considered with respect to their potential contributions to poor response or variability in response, including age, sex, race, baseline function or fitness, health status (including the presence of chronic conditions and disease severity), genetic factors, exercise modality, and exercise dose, intensity, and frequency. A summary of the characteristics evaluated in each study and their respective findings can be found in Table 4.

Age—One of the most commonly evaluated factors was age; eight articles (1887 participants) evaluated the role of age in nonresponse (Chmelo et al., 2015; Earnest et al., 2010; Kohrt et al., 1991; Lam et al., 2010; Pandey et al., 2015; Sisson et al., 2009; Skinner et al., 2001; Swift et al., 2016). Of these, 4 articles reported no relationship between age and the outcome of interest (Kohrt et al., 1991; Lam et al., 2010; Skinner et al., 2001; Swift et al., 2016). In the HERITAGE study, although older individuals had lower absolute changes in VO₂ peak, they had similar percent changes in response to exercise training (Skinner et al., 2001). Three articles (representing two studies) suggested that older adults have an increased rate of nonresponse when compared to younger adults (Earnest et al., 2010; Pandey et al., 2015; Sisson et al., 2009). Increased age was a significant predictor of nonresponse among sedentary, post-menopausal women (OR 1.45, 95% CI [1.08, 1.94]) (Sisson et al., 2009), and in the article by Earnest et al. (2010), in which the authors observed an age-attenuated exercise-related increase in peak VO₂. Women who were older (>60 years) experienced smaller increases in peak VO₂ than younger women (<55 or 55–59 years), regardless of training volume ($p < .0002$) (Earnest et al., 2010). Conversely, another study reported that older individuals actually have a decreased rate of nonresponse (Chmelo et al., 2015); older women improved to a greater degree than younger women ($r = -0.33$, $p = .04$) in a study of aerobic and resistance training in which all the study participants were 65–79 years old. Thus, there is no clear consensus on the role of age in nonresponse.

Sex—Only two articles (693 participants) specifically examined the role of sex in response to aerobic exercise (Gardner et al., 2014; Skinner et al., 2001), with inconsistent findings. In a study of 60 adults with peripheral artery disease, women were less likely to respond to a walking intervention program than men, and the women with diabetes had particularly poor response (63% did not respond, risk ratio for nonresponse was 9.2) when compared to men without diabetes (0% nonresponse) (Gardner et al., 2014). Conversely, Skinner et al. (2001)

found that females actually had a decreased risk of nonresponse; females had a greater mean percent rise in VO_2 max ($19.5\% \pm 10.6$) compared to males ($15.9\% \pm 8.5$) ($p < .01$). The role of sex in nonresponse is therefore unclear.

Race—Three studies (1104 participants) evaluated the potential role of race in nonresponse (Pandey et al., 2015; Sisson et al., 2009; Skinner et al., 2001). Although these studies had varying degrees of diversity in their samples (percent non-white ranged from 12.7% (Skinner et al., 2001) to 41.7% (Pandey et al., 2015), all three concluded that there was no significant relationship between race and responsiveness.

Body Mass Index (BMI)—Three studies (485 participants) evaluated the role of BMI in nonresponse (Osler et al., 2015; Pandey et al., 2015; Sisson et al., 2009). Two articles reported no relationship between BMI and nonresponse in individuals who were overweight or obese indicated (Pandey et al., 2015; Sisson et al., 2009). A third article, reporting the results of a study enrolling individuals with impaired glucose tolerance found the opposite effect; individuals who responded to the exercise intervention (response = impaired glucose tolerance at baseline resolved at follow-up) had a lower BMI at baseline than those who did not respond (38.4 kg/m^2 vs. 34.8 kg/m^2) (Osler et al., 2015). Therefore, there is no clear role of BMI in the response of participants to aerobic exercise interventions.

Health status—The influence of comorbidities appears to vary greatly depending on the comorbid condition being evaluated and the study outcome. Nine articles (2869 participants) evaluated the role of a specific condition or measure of disease severity in the prevalence of nonresponse (Chmelo et al., 2015; Gardner et al., 2014; Lam et al., 2010; Luo et al., 2017; Mentz et al., 2013; Osler et al., 2015; Pandey et al., 2015; Swift et al., 2016; Yalamanchi et al., 2016). Two articles (100 participants) evaluated the role of diabetes in nonresponse, and both reported that the presence of diabetes was a risk factor for nonresponse in VO_2 peak (Chmelo et al., 2015) and physical function (Chmelo et al., 2015; Gardner et al., 2014). However, the duration of diabetes and insulin use were unrelated to nonresponse in VO_2 peak (Pandey et al., 2015). Chmelo and colleagues (2015) found a tendency for improvement in usual gait speed to be greater in individuals without diabetes than those with diabetes.

The three studies (394 participants) evaluating the role of blood glucose control at baseline in nonresponse had conflicting results, although glucose control was defined differently between studies. While one study found that fasting blood glucose at baseline was not related to risk of nonresponse (Swift et al., 2016) another found that poorer blood glucose control at baseline (determined using an oral glucose tolerance test) was associated with poor response to a low-intensity, unsupervised walking intervention (Osler et al., 2015). Results of the third study (Yalamanchi et al., 2017) found that individuals with higher fasting blood glucose at baseline actually had greater relative increases in lean mass and greater decreases in fat mass than individuals with lower fasting blood glucose.

In addition to considering the role of diabetes and baseline blood glucose (fasting and glucose tolerance) in nonresponse to aerobic exercise, a variety of other health conditions were evaluated in studies included in this review. In two secondary analyses of the HF-

ACTION study, researchers found that among older adults with heart failure, neither comorbid chronic obstructive pulmonary disease (Mentz et al., 2013) nor atrial fibrillation at baseline (Luo et al., 2017) were associated with a decreased response to exercise training. Additionally, the presence of hypertension, back pain, osteoporosis, and arthritis, were unrelated to nonresponse (Chmelo et al., 2015). In one study (52 participants) evaluating outcomes of an exercise program for individuals who had an ischemic stroke, smaller lesions and having had a more recent stroke were associated with decreased nonresponse (Lam et al., 2010). Thus, the role of comorbid conditions seems to vary based on the study sample and outcome being assessed.

Baseline function or fitness—Results of the included studies suggest mixed evidence with respect to the role of baseline function or fitness in the risk for nonresponse. Six articles (1584 participants) addressed the potential role of initial fitness (Chmelo et al., 2015; Kohrt et al., 1991; Pandey et al., 2015; Sisson et al., 2009; Skinner et al., 2001; Swift et al., 2016). Three of these articles suggested that initial fitness, either with respect to baseline oxygen consumption (Kohrt et al., 1991; Pandey et al., 2015) or objectively-measured level of physical activity (Swift et al., 2016), was not related to the risk of nonresponse. However, the results of the other three studies indicated that a greater improvement in VO_2 (and thus lower risk of nonresponse) was associated with poorer fitness at baseline (Chmelo et al., 2015; Sisson et al., 2009; Skinner et al., 2001); individuals who had poorer aerobic fitness at baseline were less likely to be nonresponders than individuals with higher aerobic fitness at baseline.

Adherence—Of the included articles, five (1711 participants) examined the role of adherence to the exercise intervention (i.e., fidelity to the prescribed volume of exercise) in the prevalence of nonresponse (Chmelo et al., 2015; Fielding et al., 2007; Leifer et al., 2014; Swift et al., 2016; van Gool et al., 2005). Of these, two of the included articles suggested there was no relationship between adherence and nonresponse (Chmelo et al., 2015; Swift et al., 2016). For example, in the article by Chmelo and colleagues (2015), adherence was not associated with absolute change or percent change in any functional variable (including VO_2 peak) in response to aerobic exercise. Overall adherence was high (86%) and 78% of participants had an adherence of 80% or higher. Similarly, in the study by Swift and colleagues (2016), exercise adherence rates were similar between participants who achieved clinically meaningful levels of weight loss (99.3%) and those who did not (97.5%). The authors reported that the difference in response also did not appear to be caused by compensatory responses in non-exercise physical activity, although sedentary time and energy expenditure were not measured. It is important to note that for these analyses, individuals with adherence below a certain level (<80% in the study by Chmelo and colleagues and <85% in the study by Swift and colleagues) were excluded. In the situations in which individuals with low adherence were not excluded, however, lower adherence was associated with an increased risk of nonresponse (Fielding et al., 2007; Leifer et al., 2014; van Gool et al., 2005).

Exercise modality, frequency, duration, and intensity—Three articles (757 participants) evaluated the role of the prescribed exercise type and volume in the risk of

nonresponse (Church et al., 2009; Swift et al., 2016; Kohrt et al., 1991). Two articles (one study), in which the exercise modalities included treadmills and cycle ergometers, suggested that increased exercise volume (at the same intensity) was associated with a decreased risk of nonresponse (Church et al., 2009; Swift et al., 2016). However, this was only true for changes in oxygen consumption. Overall, response rates with respect to VO_2 improved with increasing exercise intensity. Nonresponse rates were 44.9%, 23.8%, and 19.3% in the 4, 8, and 12 kcal/kg/week groups, respectively (Sisson et al., 2009). Lower doses of exercise were actually more effective in producing weight loss than higher doses, however, this may be due to metabolic compensation (Church et al., 2009). One study found no relationship between exercise volume and nonresponse (Kohrt et al., 1991). Kohrt and colleagues also reported no relationship between exercise intensity and risk of nonresponse, however, it should be noted that the range of intensity of the exercise was not reported. Additionally, in all three articles, the reported analysis was conducted only after excluding individuals who did not adhere to the protocol, which significantly limits the ability to determine the role of different exercise modalities, frequencies, etc., on response to exercise among participants who did not reach the authors' threshold for adherence.

Genetic factors—Only one study (14 participants) evaluated the potential role of genetic factors in outcomes of aerobic exercise with respect to nonresponse (Osler et al., 2015). The results of the study by Osler et al. (2015) suggested that while there was an increase in the expression of specific genes with a role in mitochondrial biogenesis, lipid metabolism, and transcription among those who responded to the exercise intervention, these individuals did not have a different level of expression of these particular genes at baseline when compared to those who did not respond to the intervention. Thus, it is unclear to what degree genetics influences outcomes in older adults, many of whom have multiple chronic conditions.

Rating of Quality and Risk of Bias

The risk of bias of each of the included articles is reported in Table 5. Most of the articles had potential bias related to allocation concealment, as they failed to blind participants, study personnel, and data collectors to group assignments. Selective reporting was also a possible bias. Of particular concern for bias related to the assessment of nonresponse is the study by Kohrt et al. (1991) in which study participants were able to choose whether they were in the exercise or control group, which could have biased their outcomes. Several articles also reported substantial rates of attrition, ranging from 11% (Swift et al., 2016) to 39% (Kohrt et al., 1991), but did not discuss how this could influence their conclusions regarding response or nonresponse. Finally, of concern is the reporting in the study by Skinner and colleagues (2001), as they report a substantial amount of variability, including “high, medium, and low responders,” but do not describe the number of participants in each group, nor how the categories of response were derived. Thus, the methodological quality and risk of bias are potentially of concern, but are difficult to determine based on the reported study details.

Discussion

This review identified 17 articles that reported the prevalence of nonresponse and factors related to nonresponse to aerobic exercise interventions among older adults. This review also highlighted a significant shortage of studies in which variability in response among older adults, as well as the role of factors such as baseline function and comorbid conditions in response have been evaluated. Given the variability in definitions of nonresponse and outcomes evaluated, there is limited ability to compare studies, and thus develop interventions that specifically target individuals or study characteristics that could have a meaningful impact on nonresponse to aerobic exercise among older adults.

Despite these issues, a few key conclusions can be drawn from the available research. First, is the importance of considering the outcome variable and definition of response that is used when describing nonresponse, as estimates of nonresponse vary greatly based on the outcome of interest. For example, several types of nonresponse were observed in the Dose-Response to Exercise in post-menopausal Women (DREW) study, including the achievement of clinically meaningful weight loss, achievement of predicted weight loss, and improvement in VO_2 peak (Church et al., 2009; Earnest et al., 2010; Swift et al., 2016). The inclusion of four articles reporting different analyses from one study provided the opportunity to examine how conclusions on response and nonresponse may differ based on the outcome of interest. When evaluating nonresponse, the outcome and specific criteria indicative of a meaningful response should be defined *a priori* based on the theoretical or conceptual framework of the proposed study.

The discussion of what nonresponse is and what it is not is also a key issue raised by this review. A consistent finding among the studies is that individuals who did not adhere to the prescribed exercise were more likely to see little or no benefit (Fielding et al., 2007; Leifer et al., 2014; van Gool et al., 2005). This was not the case, however, in studies in which individuals with low adherence were excluded. Once adherence reached a certain threshold (>80% or 85%), it appears to be no longer related to study outcomes (Chmelo et al., 2015; Swift et al., 2016). This is an important factor to consider when evaluating the evidence, as excluding individuals with low adherence may result in inflated improvements in outcomes, possibly driven by the healthier or less complex participants, and could mask other factors that affect nonresponse.

Despite the relationship between adherence and nonresponse present at low levels of adherence, it is also important to note that adherence is fundamentally not a part of nonresponse. Nonresponse and poor response do not refer to responsiveness in individuals who have not received the intended dose of a given intervention due to nonadherence, withdrawal from the study, or limitations of participation due to other factors. Similarly, nonresponse is not caused by an ineffective intervention. Rather, nonresponse is characterized by having received the intended dose of an intervention that is effective and not having the expected response. Nonresponse is therefore not lack of adherence or the interference of other issues such as lack of protocol progression or other failures in the intervention delivery. Although defined differently among different populations and types of studies, a proposed definition of nonresponse is “a physiological lack of change or lack of

change in the expected magnitude or direction of a specific outcome variable when the participant adheres to a potentially therapeutic prescribed dose of exercise.” Additionally, nonresponse is context-specific, and thus, nonresponse to one specific exercise protocol in one setting does not guarantee nonresponse in other types of exercise protocols (Hautala et al., 2006).

The problem of failing to accurately and consistently define nonresponse is not unique to studies of older adults. The lack of a consistent definition of nonresponse has been highlighted by others in examination of studies of young adults (Scharhag-Rosenberger et al., 2012). In some studies, a fixed proportion of participants with the lowest training response were classified as nonresponders, regardless of the magnitude of change in the outcome of interest (Timmons et al., 2010; Volvaard et al., 2009), while others have considered changes that are less than two standard errors of the mean from baseline as nonresponse (T. P. Higgins, et al., 2015). Scharhag-Rosenberger and colleagues (2012) proposed that nonresponse should be defined as “individuals who improve by not more than the biological variability of the respective variable.” Therefore, there remains lack of consistency as to how nonresponse should be defined, and as in younger adults, there are many factors that could be related to an individual not demonstrating benefit from an exercise program and nonresponse is a unique phenomenon that requires further study.

A second key conclusion is that the phenomenon of nonresponse, while certainly not unique to older adults, may indeed be more prevalent among older adults than is observed in studies of younger individuals (Karavirta et al., 2011; Newton et al., 2002). Estimates of nonresponse among the included studies were quite variable (1.4–63.4%) (Skinner et al., 2001; Sisson et al., 2009) and, on average, may be slightly higher than that observed among younger individuals. The prevalence of nonresponse reported in two recent studies of young adults was 17–19% (Gurd et al., 2016; T. P. Higgins et al., 2015). However, age is not consistently linked to response in VO_2 , thus, further evaluation and consideration of factors that could influence poor response among older adults is warranted.

Overall, there is mixed evidence with respect to factors related to response or nonresponse in VO_2 peak or VO_2 max to aerobic exercise among older adults. These factors and the strength of the evidence associated with each are illustrated in Figure 2. While none of the factors have strong evidence to suggest they have a significant role in nonresponse to aerobic exercise among older adults, there are some conclusions that can be drawn from the available data. First, the strength of the evidence is low, but the available studies indicate that age, sex, race, and BMI have little to no influence on nonresponse. This is consistent with the findings of a review that addressed sources of inter-individual variability in young adults (Bouchard & Rankinen, 2001).

There is also some evidence (low strength) to support a relationship between diabetes and nonresponse, as both of the studies that evaluated the role of diabetes found that individuals with the condition had an increased risk of nonresponse (Chmelo et al., 2015; Gardner et al., 2014). Third, there is evidence (moderate strength) to suggest a role of initial fitness in nonresponse, in that individuals with lower initial fitness or function had a decreased risk of nonresponse. While the increased rate of nonresponse among individuals who are high

performing at baseline could be related to a ceiling effect, it appears that individuals who have the greatest room for improvement, particularly with respect to physiological variables, may have more potential to improve if they are able to fully participate in an exercise program of adequate intensity and duration. Additionally, despite a substantial amount of work exploring genetic determinants of trainability or exercise response in young adults (Bouchard et al., 2011; Bray et al., 2009; Ghosh et al., 2013; Wolfarth et al., 2014), the presence of chronic conditions are likely to confound outcomes of these types of studies in older adults. Thus, it is unknown to what degree genetics influences outcomes of aerobic exercise training in older adults.

The limited results of this review are consistent with available literature in younger populations. The incidence of nonresponse appears to be highest in protocols with the lowest training volume (Gurd et al., 2016), while more positive effects were found among prolonged exercise training protocols. In middle-aged adults, there is some evidence to suggest that individuals who did not respond to an aerobic intervention (with respect to VO_2 peak) may have improvements in VO_2 peak with resistance training (Hautala et al., 2006). Thus, it is possible that there are no absolute nonresponders with respect to VO_2 peak, rather, there are specific study characteristics that influence response for individuals (Churchward-Venne et al., 2015). Some individuals may require a different modality, greater intensity, or greater volume of exercise to see benefit. The key to addressing this issue is to conduct studies specifically examining nonresponders, and through more complex study designs, evaluating if response changes when the interventions is modified in one or more meaningful ways.

In addition to the factors that have been evaluated thus far, there are several variables that have not been considered that may play a key role in responsiveness to aerobic exercise that should be included in future research. First, none of the studies evaluated the role of psychosocial factors, such as motivation or self-efficacy for exercise in response to the intervention. These factors have been shown to be linked to nonresponse in a cohort of middle-aged women participant in an aerobic walking intervention (Nies & Sun, 2008), and could be key factors in nonresponse among older adults as well. Second, there is a need to evaluate other comorbid conditions, including geriatric syndromes, that could influence response, such as presence of chronic pain, history of falls, and frailty, as these factors could influence an individual's response. Third, only one of the studies (DREW) included an assessment of free-living physical activity outside of the exercise intervention that could allow for consideration of the potential role of sedentary time in outcomes of aerobic exercise programs. Research suggests that some exercise intervention participants exhibit a compensatory behavioral response by substituting their habitual free-living physical activity with the supervised exercise intervention, which results in no change or a net increase in participants' sedentary time. No change or an overall increase in sedentary time could therefore be an important factor in nonresponse (Herrmann et al., 2015; Kozey-Keadle et al., 2014). Finally, additional work is needed to evaluate the potential role of genetic factors in exercise response among older adults. While there are many candidate genes that play a role in adaptation to exercise among young adults (Bray et al., 2009), the potential implications of these genetic determinants later in life have not been examined.

In addition to participant and intervention characteristics, study quality and risk of bias may have also had a role in the conclusions drawn from this review. A common problem related to quality of the articles was the strategy used to address incomplete or missing data. Given that few studies were designed to specifically examine factors related to nonresponse to exercise interventions, many of the articles were reports of secondary analyses. Thus, reporting of study characteristics was sparse and, unfortunately, many studies simply excluded participants with incomplete outcome data. While this may have been appropriate since two data points are necessary to evaluate changes that occur as the result of an intervention, there is very little discussion of the implications of these decisions with respect to the characteristics of those who did not complete all testing. Given that adherence, motivation, self-efficacy for exercise, and comorbid conditions could affect response and are also commonly cited reasons for incomplete data or withdrawal from an exercise studies (Jette et al., 1998), this presents a significant problem for this type of analysis and exposes an area in which additional research is needed.

Implications for Health Care Providers and Fitness Professionals

Although the specific implications of these findings have not been established, for changes in practice cannot be firmly established from this single review, this review provides insight into factors and important considerations for health care providers and fitness professionals who work with older adults in implementing exercise programs. Given the variability in response observed among older adults, there are several characteristics unique to older adults that should be considered, including the contribution of accumulation of comorbidity, polypharmacy, and disability that could influence outcomes. Chronic conditions and geriatric syndromes frequently co-occur in older adults (Lee, Cigolle, & Blaum, 2009) and are strongly related to disability (Chaudhry et al., 2010). In a resistance exercise training study, the development of new medical conditions was one of the strongest predictors of adherence (Jette et al., 1998) and so, comorbid conditions could confound (or be highly correlated with) adherence and make teasing out individual effects difficult. This is also an important factor to consider when measuring and analyzing adherence data from trials with older adults. In the LIFE pilot study, illness/health problems were the most commonly cited reasons for missing center-based sessions (Fielding et al., 2007). Given this relationship, it is important to include assessment of chronic conditions and geriatric syndromes in the evaluation of nonresponse among older adults, given their potential impact on outcomes of aerobic exercise programs.

Considering what constitutes a meaningful response or nonresponse is also important as older adults may experience substantial changes in function in a short period of time. An excellent example is the work by Leifer et al. (2014), a secondary analysis of data from the HF-ACTION study. The authors defined nonresponse based on the natural changes in disease course observed by a control group, and determined that a negative change in VO_2 peak of 2 SD of the change observed in the control group was considered meaningful. Using a strategy such as this to define nonresponse, rather than simply a lack of change in the absolute value of a variable, could help ensure meaningful change, and not simply a numerical difference that does not affect the individual. Finally, it is important to consider that not all modalities are effective for every individual. By acknowledging the issue of inter-

individual variability in response to aerobic exercise, health care providers and fitness professionals can work with their patients or clients to consider individual characteristics, limitations, and goals when developing or modifying an existing program of exercise to maximize an individual's potential gain.

Implications for Future Research

Regarding implications for future research, best practices to ensure accurate assessment of variability in response should include multiple baseline and follow-up assessments. This will reduce the risk that initial levels of outcome variables are the result of random variability or an individual's health, motivation, or other factors on a given day. It is also important, as was previously discussed, to set a reasonable threshold for declaring an individual to be a negative responder. This is particularly critical given day-to-day biological variability and technical variations in cardiopulmonary exercise testing. The inclusion of a control group can help with setting this threshold, particularly in individuals with chronic disease, so one can determine the trajectory function or fitness that occurs as part of the natural course of a disease and that which may be due to an adverse response to training (Leifer et al., 2014). This will also help ensure that the observed variability in response is related to an actual difference, not random error.

Researchers should also consider the inclusion of secondary outcomes to investigate changes beyond the primary endpoint (e.g., improvement in HbA1c without improvement in cardiorespiratory fitness (Pandey et al., 2015)). Nonresponse represents a failure of just one potential adaptation to training, and thus it is plausible that participants undergo other favorable changes to training. Researchers may also wish to consider a repeated crossovers, sequential multiple assessment randomized trial (SMART), or a multiphase optimization strategy trial (MOST) design (Collins, Murphy, & Strecher, 2007) to further investigate these issues. These designs are uniquely suited to evaluate the prevalence of and factors related to nonresponse, given their inclusion of different study phases to identify, refine, and confirm the utility of intervention components, or empirically identify the best tailoring variables and decision rules for an adaptive intervention. These strategies may allow an individual participant to undergo two or more distinct periods of training and lack of training to estimate the individual participant's variability associated with each condition. While these study designs are costly and challenging to implement, they could yield valuable information to further understand the phenomena of nonresponse.

Conclusion

In summary, inter-individual variability in response to aerobic exercise interventions is prevalent among older adults and presents a significant issue for health care providers, fitness professionals, and researchers as they work to help older adults achieve optimal benefit from exercise. The results of this review provide insight into factors and considerations for aerobic exercise programs for older adults, but clear implications for implementation and delivery of these programs have not been established. Further research is needed to evaluate specific mechanisms that could explain why individuals with certain characteristics tend to have a poorer response to aerobic interventions, and develop strategies

to tailor interventions. By further considering the phenomenon of nonresponse in work with older adults and developing interventions that allow for modification of components to help more individuals respond, we can assist older adults in attaining the positive benefits of exercise.

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Figure 1.
PRISMA flow diagram of article identification, screening, and selection.
Note. *Representing 12 unique studies.

Figure 2.

Conceptual model outlining factors with little to no influence and a potential influence on responsiveness of VO_2 peak as well as those that have not been evaluated in aerobic exercise studies with older adults. *Note.* None of the factors studied have strong evidence to support their relationship to nonresponse to aerobic exercise.

Table 1

Sample Search Strategy Using OVID MEDLINE

No.	Query	Results
1	exp *Exercise/	82,620
2	(nonrespon* or non respon*).mp.	22,545
3	(differ* or varia* or heterogen* or predic* or individual* or determin* or moderat* or poo* or insufficien* or inadequa*) adj3 respon*).mp.	167,551
4	2 or 3	183,906
5	1 and 4	1,976
6	limit 5 to (English language and "middle aged (45 plus years)")	650

Note. .mp. denotes keyword search. exp “”/ denotes subject heading search. * Denotes a focus term (the listed term is one of the top 5 subject headings in the article). “adj3” denotes a search in which the first term is within 3 words of the second term (e.g., “differ* adj3 respon*” would capture the phrase “difference in individual response”).

Characteristics of Included Articles (N=17)

Author, year (Parent study)	Purpose/Aim(s)	Design, N (total)/ n(exercisers included in analysis), Follow-up period	Population characteristics (age, sex, additional key descriptors) [*]	Intervention	Outcome(s)
Kohrt et al., 1991	To determine the adaptive response of maximal aerobic power to endurance exercise training and if the magnitude of response is dependent on age, initial fitness, or frequency, duration, or intensity of the exercise program.	2-arm RCT (exercise, control) 229/110 9–12 months	Age: 63.7 (3.1) to 64.0 (3.1) in each group Sex: 51.8% female Healthy, 30 min aerobic activity <2 days/week	Supervised treadmill walking or running and stationary cycling/rowing	VO ₂ max
van Gool et al., 2005 (ADAPT)	To determine whether high exercise adherence improved physical function among older adults with knee osteoarthritis who were overweight or obese.	4-arm RCT (diet, exercise, diet + exercise, control) 316/134 18 months	Age: 68.5 (6.3) Sex: 72.2% female Knee osteoarthritis, overweight/obese	Supervised then transitioned to home-based walking and resistance training	Physical performance Osteoarthritis-related disability
Church et al., 2009 (DREW)	To examine actual weight loss compared to predicted weight loss (compensation) across different doses of exercise.	4-arm RCT (3 volumes of exercise training, control) 464/317 6 months	Age: 56.4 (6.3) to 57.9 (6.5) in each group Sex: 100% female Post-menopausal women, sedentary, overweight/obese, elevated BP	Supervised treadmill walking and stationary cycling	Compensation (predicted - actual weight loss) Waist circumference
Sisson et al., 2009 (DREW)	To examine predictors of VO ₂ max nonresponse after exercise training in post-menopausal women.	4-arm RCT (3 volumes of exercise training, control) 464/310 6 months	Age: 56.3 (6.0) to 58.0 (6.5) in each group Sex: 100% female Post-menopausal, sedentary, overweight/obese, elevated BP	Supervised treadmill walking and stationary cycling	VO ₂ peak
Earnest et al., 2011 (DREW)	To examine the effect of age on VO ₂ peak responsiveness.	4-arm RCT (3 volumes of exercise training, control) 464/251 6 months	Age: 58.3 (6.3) Sex: 100% female Post-menopausal, sedentary, overweight/obese, elevated BP	Supervised treadmill walking and stationary cycling	VO ₂ peak
Swift et al., 2016 (DREW)	To determine response rates for clinically significant weight loss following different aerobic training amounts.	4-arm RCT (3 volumes of exercise training, control) 464/330 6 months	Age: 56.7 (6.5) to 58.0 (6.5) in each group Sex: 100% female Post-menopausal, sedentary, overweight/obese, elevated BP	Supervised treadmill walking and stationary cycling	Clinically significant weight loss VO ₂ peak
Pandey et al., 2015 (HART-D)	To evaluate the impact of exercise training on metabolic parameters among participants with DM who do not improve their cardiorespiratory fitness with training.	4-arm RCT (aerobic, resistance, aerobic + resistance, control) 262/161 9 months	Age: 55.2 (8.1) to 57.6 (7.7) in each group Sex: 62% female Type 2 DM	Supervised aerobic (type not specified) and resistance exercise	Hemoglobin A1c VO ₂ peak
Skinner et al., 2001 (HERITAGE)	To examine the contributions of sex, race, age, and initial fitness on	Single group pre-test post-test study	Age: 55.7 (4.1) in older age group (50–65 y) Sex: 43.2% female	Supervised stationary cycling	VO ₂ max

Author, year (Parent study)	Purpose/Aim(s)	Design, N (total)/ n(exercisers included in analysis), Follow-up period	Population characteristics (age, sex, additional key descriptors)	Intervention	Outcome(s)
	the response of VO ₂ max to a standardized exercise training program.	633/633 (118 older adults) 5 months	Families, healthy, sedentary		
Mentz et al., 2013 (HF-ACTION)	To investigate the clinical characteristics, exercise training response, and outcomes in patients with heart failure and COPD.	2-arm RCT (exercise, control) 2331 (2311 with documented COPD status)/1172 2.5 years	Age: median 59 (IQR 51 – 68) (no COPD group) and median 64 (IQR 56 – 71) (COPD group) Sex: 29% female (no COPD group) and 25% female (COPD group) Left ventricle ejection fraction 35% with optimal medical/device therapy	Supervised walking or stationary cycling	Hospitalization/mortality Time to CV death/hospitalization, CV mortality VO ₂ peak
Leifer et al., 2014 (HF-ACTION)	To estimate the proportion of heart failure patients participating in a training program who had negative response to aerobic exercise training.	2-arm RCT (exercise, control) 2331 (1870 with baseline and follow-up stress tests available)/972 3 months	Age: median 59 (10 th percentile 43, 90 th percentile 75) Sex: 28% female Left ventricle ejection fraction 35% with optimal medical/device therapy	Supervised walking or stationary cycling	VO ₂ peak
Luo et al., 2017 (HF-ACTION)	To examine whether outcomes of exercise training in individuals with heart failure differed according to atrial fibrillation status.	2-arm RCT (exercise, control) 2331 (1984 with atrial fibrillation or sinus rhythm at baseline)/990 2.6 years	Age: median 58.5 (IQR 50.4 – 67.3) Sex: 30.1% female Left ventricle ejection fraction 35% with optimal medical/device therapy 17% with atrial fibrillation based on medical history or cardiopulmonary exercise test	Supervised walking or stationary cycling	Hospitalization/mortality Time to CV death/hospitalization, CV mortality VO ₂ peak
Fielding et al., 2007 (LIFE-P)	To examine the effects of a physical activity intervention compared with health education control on measures of disability risk in sedentary older adults.	2-arm RCT (physical activity, control) 424/213 12 months	Age: 76.5 (4.2) Sex: 68.5% female Sedentary (<20 min/week of structured physical activity), high risk of falling	Walking (primary), strength, flexibility, and balance training	Physical function
Yalamanchi et al., 2016 (SHAPE-2)	To investigate the relationship of baseline fasting glucose to the degree of muscle gains and fat loss following exercise training in individuals with type 2 DM.	2-arm RCT (exercise, control) 140/50 6 months	Age: 58 (5.1) Sex: 34% female Type 2 DM treated with diet or oral medications only (no insulin), treated hypertension or untreated suboptimal BP (SBP 120–159, DBP 85–99)	Supervised treadmill, stair stepper, or stationary bike and resistance training	Body composition (fat and lean mass) Muscle strength (1 repetition maximum)
Lam et al., 2010	To identify predictors of therapy response among participants in an aerobic treadmill exercise program for stroke survivors.	Pooled data from 2 2-arm RCTs (exercise, control) 128/52 3–6 months	Age: 66.8 (1.1) Sex: 34.6% female First-ever ischemic stroke 6 months prior to enrollment, able to walk for 3 min at 0.1 meters/s without support	Supervised treadmill walking	Walking velocity VO ₂ peak

Author, year (Parent study)	Purpose/Aim(s)	Design, N (total)/ n(exercisers included in analysis), Follow-up period	Population characteristics (age, sex, additional key descriptors)	Intervention	Outcome(s)
Gardner et al., 2014	To determine if sex and diabetes are factors in response to exercise rehabilitation in patients with claudication.	2-arm RCT (home- based exercise, supervised exercise) 80/60 3 months	Age: 66.0 (12.0) Sex: 53.3% female PAD and lifestyle-limiting claudication	Intermittent treadmill walking	Claudication onset time Peak walking time
Chmelo et al., 2015	To describe inter-individual variability in physical function responses to supervised resistance and aerobic training interventions in older adults	2-arm RCT (aerobic, resistance) 95/40 5 months	Age: 69.0 (3.6) Sex: 78% female Healthy, overweight/obese older adults	Supervised treadmill walking	VO ₂ peak Mobility
Osler et al., 2015	To determine if clinical improvements in glucose control after low-intensity exercise in individuals with impaired glucose tolerance are associated with alterations in skeletal muscle gene expression.	Single group pre-test post-test 14/14 4 months	Age: 57.6 (SEM 4.3) to 62.2 (SEM 1.4) Sex: 42.9% female Sedentary, overweight, impaired glucose tolerance	Nordic walking	Glucose tolerance via oral glucose tolerance test VO ₂ max

Note.

* Reported as mean (SD) in years unless otherwise noted.

BP = Blood Pressure; CI = Confidence Interval; CV = Cardiovascular; COPD = Chronic Obstructive Pulmonary Disease; DBP = Diastolic Blood Pressure; DM = Diabetes Mellitus; IQR = Inter-Quartile Range; PAD = Peripheral Artery Disease; RCT = Randomized Controlled Trial; SEM = Standard Error of the Mean; SBP = Systolic Blood Pressure; SPPB = Short Physical Performance Battery.

Table 3

Definition and Prevalence of Nonresponse

Author, Year (Parent study)	Definition of “nonresponse/poor response”	Prevalence of nonresponse/Variability in response
Kohrt et al., 1991	Not reported	Not reported; range of change in VO ₂ max was 0–42%
van Gool et al., 2005 (ADAPT)	Not reported	Not reported
Church et al., 2009 (DREW)	Not reported	Not reported; large degree of heterogeneity in individual weight changes in all three groups
Sisson et al., 2009 (DREW)	Change in VO ₂ max from baseline to follow-up of 0 mL/kg/min	44.9%, 23.8%, and 19.3% of the 4, 8, and 12 kcal/kg/week group, respectively, were nonresponders Overall range of change in VO ₂ max was –33.2% – 76%
Earnest et al., 2011 (DREW)	Not reported	Not reported
Swift et al., 2016 (DREW)	Lack of achievement of clinically significant weight loss (CWL) (< 5% from baseline) or modest weight loss (MWL) (< 3% but <5% from baseline)	72.8% did not achieve either CWL or MWL
Pandey et al., 2015 (HART-D)	Change in VO ₂ peak from baseline to follow-up of <5%, 5% considered clinically meaningful	63.4% did not achieve a clinically meaningful response in VO ₂ peak
Skinner et al., 2001 (HERITAGE)	Not reported	“there were high, medium, and low responders over a wide range of baseline values” It appears that at least 9 individuals (1.4%) had a change in VO ₂ max of 0.
Mentz et al., 2013 (HF-ACTION)	Not reported	Not reported
Leifer et al., 2014 (HF-ACTION)	Decrease in VO ₂ peak of 2 SD more than that observed in control group	9 participants (0.5%) had negative response
Luo et al., 2017 (HF-ACTION)	Not reported	Not reported
Fielding et al., 2007 (LIFE-P)	Not reported	Not reported
Yalamanchi et al., 2016 (SHAPE-2)	Lack of metabolic improvement after exercise	Not reported
Lam et al., 2010	Not reported	Not reported
Gardner et al., 2014	No change or decrease in claudication onset time (COT) and peak walking time (PWT) from baseline to follow-up	COT: Females with DM: 63%; Females without DM: 19%; Males with DM: 0%; Males without DM: 0% PWT: Females with DM: 44%; Females without DM: 19%; Males with DM: 22%; Males without DM: 5%
Chmelo et al., 2015	Change in VO ₂ peak from baseline to follow-up of 0 mL/kg/min	4 participants (12.9%) had no improvement in VO ₂ peak. Individual absolute value increases range from 0.4–4.3 mL/kg/min; 16% had no improvement in timed walking, 25% had no improvement in gait speed, and 28% had no improvement in chair rise time; 32% who had a baseline SPPB score <12 (room to improve) did not improve
Osler et al., 2015	Impaired glucose tolerance (IGT) (>7 mmol/L) at follow-up	5 participants (35.7%) had IGT at follow-up

Note. DM = Diabetes Mellitus; SPPB = Short Physical Performance Battery.

Table 4

Participant/Intervention Characteristics Examined and Relationship to Nonresponse

Author, Year (Parent study)	Factors and Relationship to Response/Nonresponse
Kohrt et al., 1991	<ul style="list-style-type: none"> <i>Age</i>: no significant association between improvement and age ($r = -.13$, $p = \text{NR}$), rate of increase not dependent on age <i>Initial fitness</i>: small and nonsignificant association between initial VO_2 max and change in VO_2 max (men $r = .04$, women $r = -.23$) <i>Exercise frequency, duration, intensity</i>: no relationship
van Gool et al., 2005 (ADAPT)	<ul style="list-style-type: none"> <i>Adherence</i>: increased adherence associated with improved walking distance at 6 months ($p = .002$) and 18 months ($p < .001$) and with disability at 6 months ($p = .001$)
Church et al., 2009 (DREW)	<ul style="list-style-type: none"> <i>Exercise volume</i>: the 12KKW group had significantly greater compensation (1.2 kg) than the 4 KKW (-0.3 kg) and 8 KKW (-0.2 kg) groups; in 4KKW group and 8 KKW group, 54.3% ($p = .009$) and 52.8% ($p = .01$) were compensators which is lower than in the 12 KKW group (72.6%)
Sisson et al., 2009 (DREW)	<ul style="list-style-type: none"> <i>Initial fitness</i>: significant predictor of nonresponse ($OR\ 2.01$, 95% $CI[1.47, 2.74]$), <i>Age</i>: significant predictor of nonresponse ($OR\ 1.45$, 95% $CI[1.08, 1.94]$), <i>Race</i>: not significant <i>Exercise volume</i>: 12 KKW group less likely to be nonresponders than 4 KKW group (74% less likely) ($OR\ 0.26$, 95% $CI[0.13, 0.51]$), 8 KKW group less like to be nonresponders than 4 KKW group (57% less likely) ($OR\ 0.43$, 95% $CI[0.23, 0.80]$) no difference between 12 KKW and 8 KKW groups <i>BMI</i>: not significant <i>Smoking status</i>: not significant
Earnest et al., 2011 (DREW)	<ul style="list-style-type: none"> <i>Age</i>: significant interaction for age by group ($p < .0002$), as age increased, percent improvement in VO_2 peak decreased; slope of improvement in VO_2 peak was significantly steeper among <55 than 60 ($p < .05$), but not different from the 55–59 group; only women under age 59 showed significant improvements in VO_2 peak in the 8KKW and 12 KKW groups
Swift et al., 2016* (DREW)	<ul style="list-style-type: none"> <i>Age</i>: age ≥ 65 years not related to weight loss or change in VO_2 peak <i>Adherence</i>: not significant, adherence similar among those who did (99.3%) and did not (97.5%) achieve CWL ($p = .215$) <i>Baseline fitness</i>: steps $<5000/\text{day}$ not related to outcome <i>Baseline fasting blood glucose</i>: $>100\text{mg/dL}$ not related to outcome <i>Exercise volume</i>: greater volume was associated with greater odds of achieving at least MWL (1.8, $CI[1.08-3.03]$), but not with achievement of CWL
Pandey et al., 2015 (HART-D)	<ul style="list-style-type: none"> <i>Age</i>: responders were younger ($p = .03$) <i>Exercise modality</i>: no difference between responders and nonresponders with respect to type of exercise (aerobic vs. aerobic + resistance) ($p = .33$) <i>Baseline fitness</i>: not related <i>Race, BMI, BP, DM duration, Insulin use</i>: not related
Skinner et al., 2001 (HERITAGE)	<ul style="list-style-type: none"> <i>Age</i>: VO_2 max was lower among older age group (when compared to 17–29 and 30–49 year groups); no significant difference in percent change among the 3 age groups; similar numbers of “nonresponders” among older and younger age groups <i>Sex</i>: females had greater mean % rise in VO_2 max <i>Race</i>: not related

Author, Year (Parent study)	Factors and Relationship to Response/Nonresponse
	<ul style="list-style-type: none"> <i>Baseline fitness</i>: no significant correlation between baseline VO_2 max and change in VO_2 max, % change in VO_2 was correlated with baseline values ($-0.37, p < .01$)
Mentz et al., 2013 (HF-ACTION)	<ul style="list-style-type: none"> <i>COPD</i>: no difference in 6 minute walk distance, duration of max test, and VO_2 peak based on COPD status, no evidence to suggest an interaction between COPD status and exercise training on mortality and other clinical outcomes (except an increased risk of CV mortality/heart failure hospitalization among those with COPD [46%])
Leifer et al., 2014 (HF-ACTION)	<ul style="list-style-type: none"> <i>Adherence</i>: among those who exercised 90 minute/week, only 2 met negative response threshold
Luo et al., 2017 (HF-ACTION)	<ul style="list-style-type: none"> <i>Atrial fibrillation</i>: no difference in VO_2 peak or 6 minute walk test distance at 3 months between those with and without atrial fibrillation; similar rates of all-cause mortality between those with and without atrial fibrillation
Fielding et al., 2007 (LIFE-P)	<ul style="list-style-type: none"> <i>Adherence</i>: at 6 months there was no difference in change in SPPB score between those who reported 150 minutes and <150 minutes of moderate physical activity, at 12 months those who reported 150 minutes moderate physical activity had a significant improvements in SPPB score (<i>OR</i> 1.22, 95% <i>CI</i> [0.82, 1.62]) compared to those who reported <150 minutes (<i>OR</i> 0.68, 95% <i>CI</i> [0.34, 1.02]), $p = .017$, adjusted for site, gender, and medical suspension
Yalamanchi et al., 2016 (SHAPE-2)	<ul style="list-style-type: none"> <i>Baseline fasting blood glucose</i>: each <i>SD</i> higher level of baseline fasting blood glucose (mean 135.5, <i>SD</i> 39.0) was associated with a significant increase in percent of total lean mass ($0.54 \pm 0.26\%$, $p = .048$) gained from baseline to follow-up; each <i>SD</i> higher level of fasting glucose at baseline was associated with significantly greater loss in percent total body fat ($-0.57 \pm 0.27\%$, $p = .04$) from baseline to follow-up
Lam et al., 2010	<ul style="list-style-type: none"> <i>Age</i>: not related <i>Disease severity</i>: relative improvement in 10 meter walking velocity higher in patients with smaller lesions and 6 minute walk velocity higher in those with more recent stroke events <i>Baseline fitness</i>: not related
Gardner et al., 2014	<ul style="list-style-type: none"> <i>Sex</i>: males improved in claudication onset time and peak walking time more than females ($p = .005$, and $p = .003$) <i>Diabetes</i>: patients without DM improved to a greater degree than those with DM ($p < .005$) <i>Exercise volume</i>: total number of strides in exercise program was associated with change in claudication onset time ($r = .268$, $p = .044$) <i>Adherence</i>: exercise time, cadence, and ambulatory volume not related
Chmelo et al., 2015*	<ul style="list-style-type: none"> <i>Age</i>: older individuals improved more ($r = -0.33$, $p = .04$) <i>Adherence</i>: not related, in analysis of only individuals with high adherence (>80%) changes in VO_2 peak ranged from -5% to 23% <i>Baseline fitness</i>: 400 meter walk time, gait speed, chair rise, and SPPB were negatively correlated with initial function (greater improvement seen in those with poorer baseline function), no relationship seen with respect to VO_2 peak <i>Hypertension, back pain, arthritis, osteoporosis</i>: not related <i>Diabetes</i>: individuals without DM improved more with respect to VO_2 peak (0.10 mL/kg/min without, 0.00 mL/kg/min with)
Osler et al., 2015	<ul style="list-style-type: none"> <i>BMI</i>: lower BMI at baseline related to NGT at follow-up <i>Disease severity</i>: baseline blood glucose (fasting and 2-h), and HbA1c were lower in IGT-NGT group <i>Genetics</i>: candidate genes related to mitochondrial biogenesis, lipid metabolism, and transcription had no difference in expression between the IGT-NGT and IGT-IGT groups; exercise training did increase expression in several of these genes post-exercise training in the IGT-NGT but not the IGT-IGT group

Note.

* Analyses excluded individuals with low adherence.

BP = Blood Pressure; BMI = Body Mass Index; CV = Cardiovascular; COPD = Chronic Obstructive Pulmonary Disease; CWL = Clinically Significant Weight Loss; CI = Confidence Interval; DM = Diabetes; IGT = Impaired Glucose Tolerance; KKW = Kilocalories per Kilogram per Week; MWL = Minimal Weight Loss; NGT = Normal Glucose Tolerance; NR = Not Reported; OR = Odds Ratio; r = Pearson Correlation; SPPB = Short Physical Performance Battery; SD = Standard Deviation.

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Table 5

Summary of Methodological Quality Using Cochrane's Risk of Bias Assessment Tool (J. Higgins & Green, 2011)

	Kohrt et al., 1991	van Gool et al., 2005 (ADAPT)	Church et al., 2009 (DREW)	Sisson et al., 2009 (DREW)	Earnest et al., 2011 (DREW)	Swift et al., 2016 (DREW)	Pandey et al., 2015 (HART-D)	Skinner et al., 2001 (HERITAGE)*	Mentz et al., 2013 (HF-ACTION)	Leifer et al., 2014 (HF-ACTION)	Luo et al., 2017 (HF-ACTION)	Fielding et al., 2007 (LIFE-P)	Yalamanchi et al., 2016 (SHAPE-2)	Lam et al., 2010	Gardner et al., 2014	Chmelo et al., 2015	Osler et al., 2015*
Random sequence generation (selection bias)	+	+	+	+	+	+	+	N/A	+	+	+	+	+	+	?	?	N/A
Allocation concealment (selection bias)	+	+	+	+	+	+	+	N/A	+	+	+	+	?	?	?	?	N/A
Blinding of participants and personnel (performance bias)	+	?	+	+	+	+	+	N/A	?	?	?	+	?	?	?	+	N/A
Blinding of outcome assessment (detection bias)	?	?	?	?	?	?	+	N/A	+	+	+	+	?	?	?	+	N/A
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other bias	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Note.

* Single group pre-test post-test study.

N/A = Not Applicable. + = High risk of bias; ? = Unclear risk of bias; - = Low risk of bias.