META-ANALYSIS: THE EFFECT OF PHYSICAL ACTIVITY ON CHOLESTEROL LEVEL IN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Background: It has been consistently showed that concentration of low-density lipoprotein cholesterol (LDL-C) increasing is associated with an increased risk of myocardial infarction and vascular death. Lack of regular exercise is a major cause of cardiovascular disease (CVD) and contributes to the pathogenesis of cardiovascular system disease via several mechanisms including atherosclerosis, which can be altered by physical activity. Lack of regular exercise is a major cause of CVD and contributes to the pathogenesis of cardiovascular system disease via several mechanisms including atherosclerosis, which can be altered by physical activity. The purpose of this study was to investigate the effect of physical activity on cholesterol level in type 2 diabetes mellitus (DM) patients.
Subjects and Method: The present systematic review and meta-analysis is structured according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). PICO framework was used to develop the inclusion and exclusion criteria for study selection, Population= type 2 DM patients, Intervention= high physical activity, Comparison= low physical activity, and Outcome= cholesterol level. Four different electronic databases were used for result retrieval: PubMed, Science Direct, Scopus, and Google Scholar. Keywords used "physical activity" OR "Exercise" AND "diabetes mellitus" OR "patients diabetes mellitus". This study included English-language studies primarily from randomized controlled trials (RCTs). Analyses performed using Review Manager 5.3.
Results: A meta-analysis involved 9 studies from United States, Australia, Italia, Finland, Belgium, United Kingdom, and Canada, resulted that high physical activity in type 2 DM patients significantly reduced cholesterol 1.21 units compared to low physical activity (SMD= -1.21; 95% CI= -2.31 to -0.12; p= 0.030).
Conclusion: High physical activity in type 2 DM patients significantly reduces cholesterol compared to low physical activity.

Keywords: physical activity, cholesterol, diabetes mellitus, physical activity, meta-analysis

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BACKGROUND

New technological discoveries help human work to be easier, and quickly completed. The negative side of technological developments is the decrease in daily physical activity (Oliveira-brochado *et al.*, 2010; Effendi *et al.*, 2014). In response, the government has determined that physical activity is one of the 10 indicators of clean and healthy living behavior (PHBS) and one of the 4 pillars of balanced nutrition (Indonesian Ministry of Health, 2014).

According to WHO, physical acti-

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vity is defined as body movements produced by skeletal muscles that require energy expenditure. The energy is obtained from the food consumed. Diet and physical activity can determine cholesterol levels in the body. The food consumed will undergo a metabolic process and produce adenosine triphosphate (ATP). ATP is energy for physical activity. The formation of ATP is adapted to physical needs, so that not all food consumed will be converted directly into ATP but some are stored in the form of cholesterol. The more physical activity you do, the more ATP you need and will cause less formation of total cholesterol and Low-Density Lipoprotein (LDL) cholesterol and an increase in High-Density Lipoprotein cholesterol (HDL) (Rodwell et al., 2015; Whitney et al., 2015).

Hossain-Alizadeh et al. (2014) stated that there was a significant relationship between physical activity and cholesterol levels. Meanwhile, a study by Moraleda et al. (2013) reported that there was no relationship between physical activity and cholesterol levels.

Physical exercise has a small but detectable effect on glycemic control and cardiovascular risk factor control for type II diabetes (Downes, 2015; Micha *et al.,* 2017). The effect of exercise on glucose control is clinically significant and is related to the effect of body weight and body composition (Abbate, 2012; Rahati *et al.*, 2014).

Various studies have been carried out with varying results around the world, but further analysis needs to be done in order to get a more convincing conclusion. Therefore, the authors are interested in conducting a systematic review with meta-analysis to identify the magnitude of the effect of physical activity on cholesterol levels in type 2 DM patients.

SUBJECTS AND METHOD

1. Study Design

This was a systematic study and meta-analysis, with the following PICO: Population (P)= Patient diagnosed with type 2 DM, Intervention (I)= high physical activity, Comparison (C)= low physical activity, and Outcome (O)= cholesterol level. Articles collected in this study were obtained from several databases including PubMed, Science Direct, Scopus, and Google Scholar. Articles were collected and selected using the PRISMA flow diagram guidelines. Articles were analyzed using the Review Manager 5.3 application.

2. Inclusion Criteria

The inclusion criteria were full text of randomized controlled trials.

3. Exclusion Criteria

Exclusion criteria were quasi-experimental, cohort, case control, and cross-sectional studies, which did not report mean and SD values, and used languages other than English and Indonesian.

4. Operational Definition of Variable

Total cholesterol is defined as the combination of the amount of HDL, LDL, and triglycerides per deciliter of blood. The measurement scale was continous.

Physical activity is any bodily movement produced by skeletal muscles that requires energy. Physical activity involves biochemical and biomechanical processes. Physical activity was

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measured using the International Physical Activity Questionnaire (IPAQ). The measurement scale was continous.

5. Study Instrument

The study was guided by the PRISMA flowchart and the quality assessment used an assessment from a randomized controlled trial (RCT) published by Centre for Evidence-Based Medicine (CEBM).

6. Data Analysis

The data in the study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots are used to determine the size of the relationship and the heterogeneity of the data. The fixed effect model is used for homogeneous data, while the random effect model is used for heterogeneous data across studies.

RESULTS

The initial search process in the database yielded 1,117 articles for physical activity on cholesterol levels, and after the deletion process of published articles, 9 of them met the requirements for a full text review (see Figure 1).

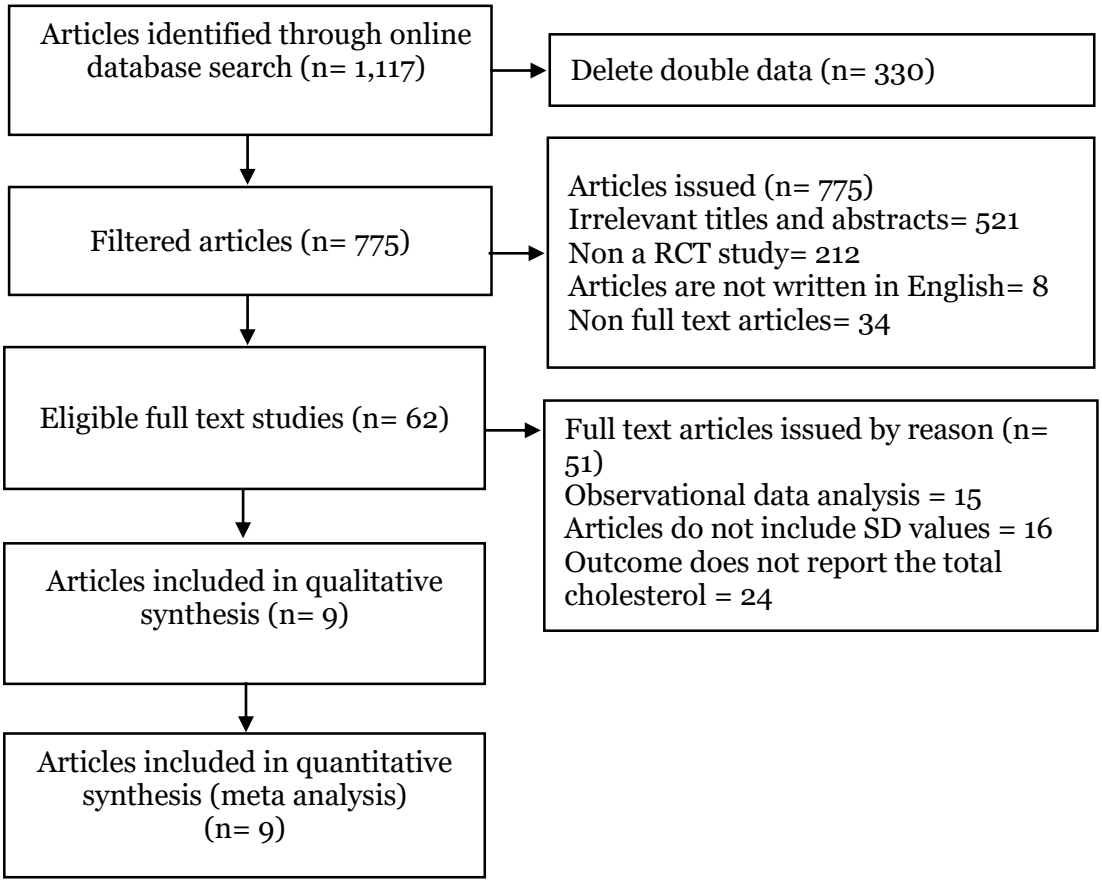

Figure 1. PRISMA Flow diagram about effectiveness of physical activity to cholesterol levels

Map of research areas regarding the effectiveness of physical activity on cholesterol levels in type 2 DM patients spread across the Americas, Europe, and Australia (see Figure 2).

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Table 1. Assessment of the quality of randomized controlled trial studies

Assessment of research quality using Critical Appraisal Questions for Randomized controlled trial (RCT) published by the Center for Evidence-Based Medicine (CEBM), is reported in the following table:

Table 1. Results of Quality Assessment of physical activity on cholesterol levels in type 2 DM patients

No	Questions	Publication (Author and year of publication)								
		Castaneda *et al.* (2002)	Crunch *et al.* (2010)	Dustan *et al.* (2002)	Goldhaber-Fiebert *et al.* (2003)	Kadoglou *et al.* (2007)	Kadoglou *et al.* (2010)	Middlebrooke *et al.* (2006)	Sigal *et al.* (2016)	Loreto *et al.* (2005)
1	Does the research address a clear research focus?	2	2	2	2	2	2	2	2	2
2	Is a randomized controlled trial suitable for answering research questions?	2	2	2	2	2	2	2	2	2
3	Are there enough research subjects to establish that the findings were intentional?	2	2	2	2	2	2	2	2	2
4	Were subjects randomly divided into experimental and control groups? If not, could this introduce bias?	2	2	2	2	2	2	2	2	2
5	Does the study use inclusion/exclusion criteria?	2	2	2	2	2	2	2	2	2
6	Were the two groups comparable at the initial stage?	2	2	2	2	2	2	2	2	2
7	Are the outcome criteria objective and unbiased?	2	2	2	2	2	2	2	2	2
8	Is the measurement method used objective and valid to measure the results? If not, was there blinding in the study?	2	2	2	2	2	2	2	2	2
9	Is the effect size practically relevant?	2	2	2	2	2	2	2	2	2
10	Are the effect estimates correct? Is there a degree of confidence interval??	0	0	2	0	0	0	0	0	0
11	Are there any confounding factors that have not been taken into account?	2	2	2	2	2	2	2	2	2
12	Can the results be applied to your research?	2	2	2	2	2	2	2	2	2
	Total score	**22**	**22**	**24**	**22**	**22**	**22**	**22**	**22**	**22**

Information:

Score 2= yes; 1= uncertain; 0= no

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Summary souce of studies selected for meta analysis

There are 9 randomized controlled trials (RCT) on physical activity as a source of meta-analysis which are described as follows:

Table 2. Description of the primary study of physical activity on cholesterol levels in type 2 DM patients

Author (Year)	Country	Study design	Number of Sample		Population	Intervention	Comparison	Outcome	Mean		SD	
			Physical activity	Control					High physical activity	Low physical activity	High physical activity	Low physical activity
Castaneda *et al.* (2002)	United States	RCT	31	31	Type 2 DM patients aged 66 years (40 women and 22 men)	High physical activity	Low physical activity	Low cholesterol levels	4.81	4.70	0.16	0.18
Dunstan *et al.* (2002)	Melbourne, Australia	RCT	16	13	Type 2 DM Patients aged 60 to 80 years	High physical activity	Low physical activity	Low cholesterol levels	-0.09	-0.5	0.8	0.8
Goldhaber-Fiebert *et al.* (2003)	Costa Rica, Central America	RCT	33	28	61 Type 2 DM patients aged 59 years	High physical activity	Low physical activity	Low cholesterol levels	-1.8	1.0	36	33
Kadoglou *et al.* (2007)	Italy, Southern Europe	RCT	30	30	60 Type 2 DM patients aged 64 years (26 men and 34 women)	High physical activity	Low physical activity	Low cholesterol levels	-18.5	7.04	8.05	2.91
Kadoglou *et al.* (2010)	Finland, Europe	RCT	25	25	50 Type 2 DM patients aged over 18 years	High physical activity, therapy with anti-diabetic drugs, and the combination of physical activity and anti-diabetic drug therapy	Low physical activity	Low cholesterol levels	-19.48	1.47	15.44	29.6
Lambers *et al.* (2008)	Belgium	RCT	17	17	46 patients with type 2 DM (17 women and 29 men)	High physical activity	Low physical activity	Low cholesterol levels	4.6	5.0	0.67	1.18

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Author (Year)	Country	Study design	Number of Sample		Population	Intervention	Comparison	Outcome	Mean		SD	
			Physical activity	Control					High physical activity	Low physical activity	High physical activity	Low physical activity
Middlebrooke *et al.* (2006)	Great Britain, Europe	RCT	22	30	59 patients with Type 2 DM aged 63 years (32 men and 27 women)	High physical activity	Low physical activity	Low cholesterol levels	4.9	5.3	0.9	1.0
Sigal *et al.* (2016)	Canada	RCT	59	62	251 Type 2 DM patients aged 39 to 70 years	High physical activity, endurance training, a combination of physical exercise and endurance	Low physical activity	Low cholesterol levels	4.79	4.86	2.25	2.06
Loreto *et al.* (2005)	Italia	RCT	34	34	Type 2 DM patient with a history of illness for at least 2 years and age 40 years	High physical activity	Low physical activity	Low cholesterol levels	-0.2	5.6	0.1	0.1

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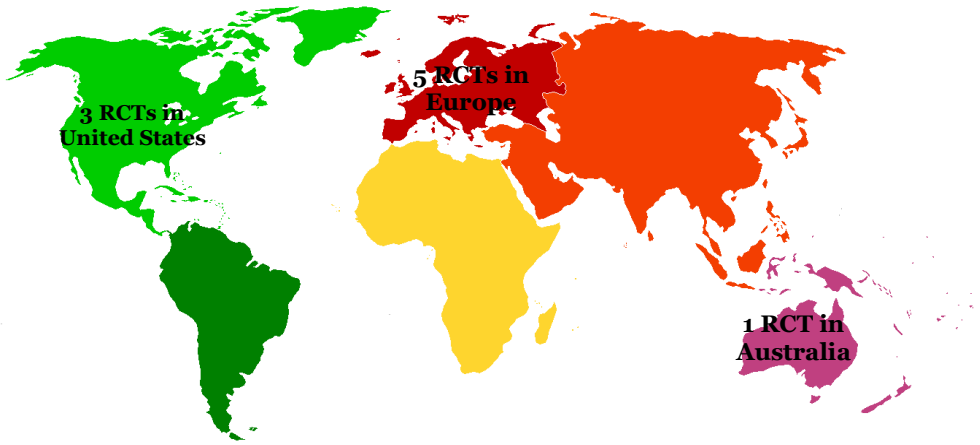

Figure 2. Map of the study area on the effectiveness of physical activity on cholesterol levels in patients with type 2 DM

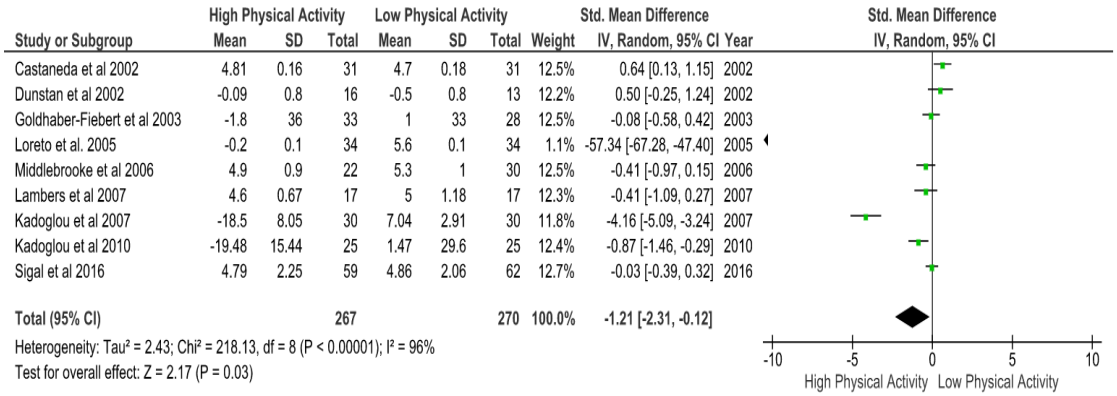

Figure 3. Forest plot of physical activity on total cholesterol in type 2 DM patients

Figure 3 shows that research related to the effectiveness of physical activity on total cholesterol in type 2 DM patients consists of 9 articles originating from 3 studies from the Americas, 5 studies from Europe, and 1 study from Australia.

The forest plot in Figure 3 shows that high physical activity can reduce cholesterol levels in type 2 DM patients. Type 2 DM patients with high physical activity have cholesterol levels as much as 1.21 units lower compared to type 2 DM patients with low physical activity, and these results are statistically significant (SMD= -1.21; 95% CI= -2.31 to -0.12; p= 0.030). this study has a Heterogeneity value of I^2= 96%, this indicates that the estimated effect between primary studies in the meta-analysis varies widely. Thus, the calculation of the average effect estimate is carried out using the random effect model approach.

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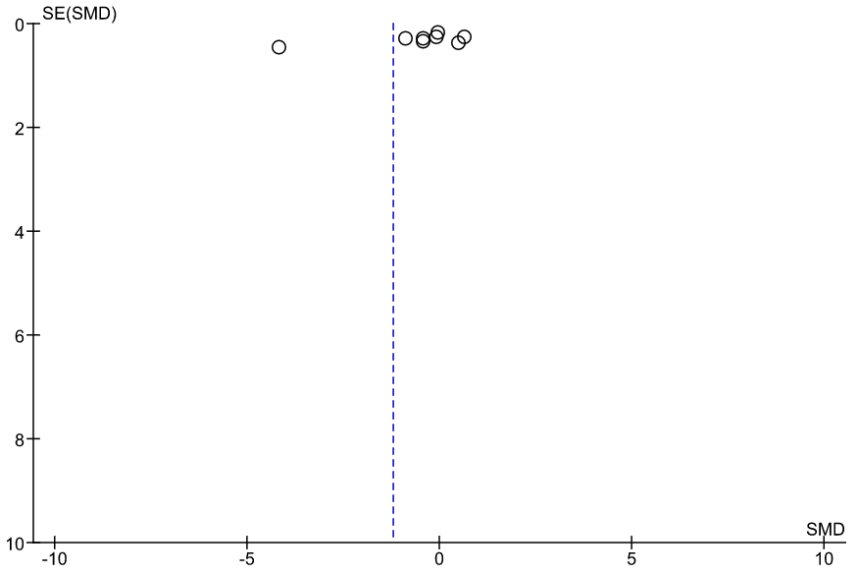

Figure 4. Funnel plot of physical activity on cholesterol levels in type 2 DM patients

The funnel plot in Figure 4 shows that the distribution of effect estimates from the primary study meta-analysis lies more to the right of the estimated mean vertical line than to the left, which indicates publication bias. Because the publication bias tends to be to the right of the average vertical line in the same direction as the location of the diamond shape in the forest plot, the publication bias tends to overestimate the effect of actual physical activity on cholesterol.

DISCUSSION

Systematic review and meta-analysis in this study were carried out with the aim of increasing the generalization of the findings and obtaining convincing conclusions from the results of various similar studies regarding the effectiveness of physical activity on cholesterol levels in type 2 DM patients. A total of 9 articles that met the criteria totaled 9 articles originating from (1) 3 studies from America, (2) 5 studies from Europe, and (3) 1 study from Australia.

A total of 9 experimental studies with RCTs as a source of meta-analysis of the effectiveness of physical activity on cholesterol levels. This study shows that high physical activity can reduce cholesterol levels in type 2 DM patients. Type 2 DM patients with high physical activity have cholesterol levels as much as 1.21 units lower compared to type 2 DM patients with low physical activity, and it was statistically significant (SMD= -1.21; 95% CI= -2.31 to -0.12; p= 0.030).

Study by Lopirinzi and Addoh (2016) shows that physical activity has a significant relationship with total cholesterol (Waloya, 2013; Lopirinzi and Addoh, 2016; Pilch *et al.*, 2016). Physical activity has an inverse relationship with LDL cholesterol levels (r= -0.28; p= 0.001). This is in line with the theory which states that food that enters the body goes through a process of digestion, absorption, and is formed into Acetyl-CoA. It will enter the krebs cycle and ATP formation occurs. The process of

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forming and transporting cholesterol throughout the body will decrease, resulting in decreased formation of Low-Density Lipoprotein (LDL).

A different study was conducted by de Munter (2011), which showed that physical activity had no relationship with HDL cholesterol levels. Theoretically states that when the formation of ATP increases, the body will compensate by forming High-Density Lipoprotein (HDL). The formation of HDL is intended to facilitate excess cholesterol in the periphery to be transported to the liver as an energy reserve. Other studies have shown that physical activity does not affect HDL cholesterol levels (Chu and Moy, 2013).

Physical activity has an important role in regulating blood glucose, protein and fat metabolism, increasing insulin action, preventing diabetes complications, increasing flexibility and muscle strength, and having a good effect on the cardiovascular system (ADA, 2014). Low physical activity is known to be associated with a 25-70% increased risk of cardiovascular disease and mortality in type 2 DM patients with an average age of 60 years when followed for 5 years (Zethelius et al., 2014). Increased physical activity is also known to reduce the risk of developing from Gestational Diabetes (GDM) to type 2 DM. In addition, regular physical activity can improve blood circulation and reduce the risk factors for type 2 DM (Damayanti, 2016).

Management of regular physical activity is urgently needed in order to improve insulin sensitivity, glycemic control, and metabolic profiles of patients and individuals who are at risk of developing type 2 DM (Aune *et al.,* 2015; ADA, 2018; Nurayati and Adriani, 2017). Management of routine and regular physical activity is urgently needed in order to improve insulin sensitivity, glycemic control, and metabolic profiles of patients and individuals who are at risk of developing type 2 DM (Lisiswanti, 2016).

This study concluded that physical activity is effective in reducing cholesterol levels in type 2 DM patients. The limitation of this research is that there is a language bias because the articles used are articles in English, thus ignoring other languages. Another limitation is the presence of search bias, because researchers only use 4 database sources, thus ignoring other search sources. This study recommends conducting further meta-analysis studies related to the effectiveness of physical activity on cholesterol levels as an effort to prevent type 2 DM with a larger number of research subjects, more countries included, and not limiting article retrieval based on language.

AUTHOR CONTRIBUTION

Fikri Dian Dinu Azizah is the main researcher who chooses the topic. Bhisma Murti and Eti Poncorini Pamungkasari explore and collect data, analyze data, and review research documents.

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This study is self-funded.

CONFLICT OF INTERESTS

There is no conflict of interest.

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