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Diabetes-specific formulas high in monounsaturated fatty acids and metabolic outcomes in patients with diabetes or hyperglycaemia

A systematic review and meta-analysis

Alejandro Sanz-París [1,2*], Pilar Matía-Martín[3], Ángela Martín-Palmero[4], Carmen Gómez-Candela[5], Maria Camprubi Robles[6]

[1]Nutrition Department of University Hospital Miguel Servet, Zaragoza, Spain

[2]Instituto Aragonés de Ciencias de la Salud (IACS)

[3]Endocrinology and Nutrition Unit, Hospital Clínico San Carlos; Medicine Department, Faculty of Medicine, Universidad Complutense de Madrid (UCM); Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

[4]Nutrition Department of Hospital San Pedro, Logroño, Spain

[5]Nutrition Department of University Hospital La Paz, Madrid, Spain

[6]Abbott Nutrition, Research and Development, Granada, Spain

***Corresponding author:** Alejandro Sanz-París. Nutrition Department. Hospital Miguel Servet. C/ Isabel La Católica, 1-3. 50009 Zaragoza, Spain. E-mail: asanzp@salud.aragon.es

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Tables: 3

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Abbreviations:

ADA: American diabetes association

ASPEN: American society of parenteral and enteral nutrition

AUC: area under curve

CI: confidence intervals

DM: Diabetes Mellitus

DM-i: patients with diabetes treated with Insulin

DM-oa: patients with diabetes treated with oral antidiabetic drugs

DSF: Diabetes-specific formula

EN: enteral nutrition

ESPEN: European society of clinical nutrition and metabolism

GV: glycaemic variability

HbA1c: glycosylated hemoglobin

HDL: high density lipoprotein

MLFU: medium- and long-term follow-up

MUFA: monounsaturated fatty acids

ONS: oral nutritional supplement

OR: odds ratio

RCT: randomised clinical trial

SD: standard deviation

SE: standard error

SMD: standardised mean difference

STDF: standard formula

TE: total energy

T2DM: type 2 diabetes

TG: triglycerides

Abstract

Objective – The aim of this study was to compare the metabolic benefits of diabetes-specific formulas (DSF) high in monounsaturated fatty acids (MUFA) with standard formulas (STDF) in adult patients with type 1, type 2 diabetes or stress-induced hyperglycaemia.

Research design and methods – A systematic review and meta-analysis were conducted through a literature search using different electronic databases from the index date to December 2018. We included randomised controlled trials that assessed the health benefits of high ~~a~~ MUFA DSF STDF. Included outcomes were glycaemic control, lipid metabolism and tolerance. Effect sizes were calculated as standardised mean differences (SMD) (<0.4 were considered small, 0.4-0.7 moderate and >0.7 large). This systematic review was registered as CRD42018108931 on Prospero.

Results – Of 385 references reviewed, 18 studies involving 845 adults met our inclusion criteria and contributed to the meta-analysis. Use of high ~~a~~ MUFA DSF compared with a STDF was associated with a statistically significant decrease in peak of postprandial glucose [SMD -1.53, 95% confidence interval (CI) -2.44 to -0.61], incremental glucose response (SMD -1.19, 95% CI -1.71 to -0.68), area under the curve of plasma insulin (SMD -0.65, 95% CI -1.03 to -0.26), mean blood glucose level (SMD -0.41, 95% CI -0.63 to -0.19), glycosylated haemoglobin (HbA1c) change (SMD -0.63, 95% CI -1.21 to -0.05), glucose variability (SMD -0.93, -1.55 to -0.31), mean administered insulin dose (SMD -0.49, 95% CI -0.85 to -0.14), mean blood triglycerides (SMD -0.34, 95% CI -0.65 to -0.03) and increase of mean blood high-density lipoproteins (SMD +0.42, 95% CI 0.08 to 0.76). Non-significant differences were found for tolerance [odds ratio (OR) 0.95, 95% CI 0.87 to 1.05].

Conclusions - This meta-analysis shows that a DSF (oral supplements and tube feeds) high in MUFA~~s~~ can improve glucose control and metabolic risk factors among patients with diabetes or stress-induced hyperglycaemia compared with a STDF.

INTRODUCTION

The use of enteral nutrition (EN) for patients with diabetes mellitus (DM) or stress~~ed~~-induced hyperglycaemia is commonly observed in different clinical settings.[1] Approximately 5% to 8% of hospitalised patients in Spain receive EN[2], and in the US, approximately 5.8% of institutionalised elderly people are fed through EN.[3] In an internal medicine facility, it has been observed that as many as 34.5% of patients using EN had blood glucose levels higher than 200 mg/dL.[4] In geriatric residences, it was reported that 50% of patients with dementia receiving EN showed glycosylated haemoglobin (HbA1c) levels greater than 7%, and of these, half were not diagnosed with DM.[5]

Metabolic control by using EN in patients with diabetes or stress-induced hyperglycaemia can be complex in clinical practice due to multiple reasons.

The increased use of EN and oral nutritional supplements (ONS) in patients with DM has resulted in a wide range of different types of diabetic-specific formulas (DSFs) currently existing on the market with a markedly variable composition in macro- and micronutrients. DSFs administered as ONS have been associated with improved health outcomes in patients with DM as well as improved nutritional status and better glycaemic control.[6] However, there is no consensus among main nutrition authorities and societies on the use of DSFs instead of standard formulas (STDFs) for patients with DM. The American Society of Parenteral and Enteral Nutrition (ASPEN) concluded that no recommendation on the use of DSFs could be made based on the results from two clinical studies.[7] On the other hand, recently published European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines recommend the use of DSFs as a part of an interventional plan for people with obesity and DM[8]. Recently, the American Diabetes Association (ADA) concluded that the effect of DSFs may be superior to STDFs to manage postprandial glucose response, HbA1c levels and insulin response.[9]

Review publications addressing the use and effectiveness of DSFs (oral supplements or tube feeds) for people with DM are scarce.[10-12] An evidence-based recommendation has been recently published on the role of EN in patients with DM or hyperglycaemia.[13] Since the last meta-analysis conducted by Elia M et al. in 2005,[10] multiple studies have been published, which have been discussed in several narrative reviews, but were not included in systematic reviews or meta-analyses. A primary challenge is that commercially available DSFs have very different compositions in terms of quality and quantity of ingredients and, especially, have different levels of carbohydrate and monounsaturated fatty acids (MUFAs).[14].

Therefore, the purpose of the present study is to develop a systematic review and meta-analysis of the studies published up to now comparing the effect of DSFs rich in MUFAs and STDFs in patients with DM or hyperglycaemia. The current article aims to provide new evidence and will help determine if the use of DSFs high in MUFAs is associated with improved health benefits related to blood glucose management, lipid metabolism, insulin requirements and gastrointestinal tolerance in patients with DM.

METHODS

Data sources and searches

A comprehensive systematic literature search was conducted through seven different electronic databases: PubMed, Cochrane Library, WHO, International Clinical Trial Register, clinicaltrials.gov, European Clinical Trial Register and Tripdatabase, from the index date to December 31, 2018.

The search key words used were: “diabetes mellitus”, “diabetic”, “stress diabetic”, “monounsaturat*”, “mono-unsaturat*”, “monounsaturated fatty acid”, “MUFA”, “enteral nutrition”, or “diabetes-specific enteral formula nutrition”, “diabetes specific feed”, “diabetes specific supplement”. The search was limited to randomised clinical trials (RCTs) published in English. The search was completed with a crosscheck from the references of the selected articles. When additional information was required, study authors were contacted directly to request such information. See supplementary material for a detailed description of the search strategy used.

Study selection and data extraction

Two of the authors of this review (ASP and PMM) evaluated the selected studies independently, and any disagreement was solved by consensus. Only RCTs and crossover studies that met the following patient inclusion criteria were selected: subjects with type 1 or 2 DM or stress-induced hyperglycaemia, on enteral nutrition and over 18 years of age. Before-after studies, uncontrolled trials and observational studies were excluded. With regard to interventions, the studies had to compare a DSF high in MUFAs versus a STDF provided as oral supplement or tube feed.[1] DSFs high in MUFAs were defined by ESPEN guidelines as those providing ≥ 20% of the total energy (TE) from MUFAs or ≥ 40% of the TE from fats as compared to a STDF.[14] Selected studies were differentiated between postprandial or medium- and long-term follow-up (MLFU) studies to perform differential analyses depending on this timeframe for the interventions studied.

Regarding efficacy measurements, it was decided that only studies reporting at least one variable related to glycaemic control or lipid control would be included, such as postprandial peak plasma glucose, postprandial insulin peak and postprandial plasma glucose increment for postprandial studies; and mean of glucose, glycosylated haemoglobin (HbA1c), glycaemic variability (GV), insulin dose, triglycerides, high-density lipoprotein cholesterol (HDL) and adverse events described for MLFU studies.

Once the studies with potential inclusion criteria were identified, full texts were downloaded and evaluated by each member of the research team, debating doubts and discrepancies. Extraction of data from the included studies was done using tables with sections to be filled in by the members of the research team, referring to the specific characteristics of the studies and outcomes analysed as follows: author and year of publication; methods (study design: parallel or crossover); participants (sample size, type of DM or stress hyperglycaemia, treatment with insulin or oral antidiabetic drugs); intervention (duration: postprandial study or medium/long-term intervention), route of administration (oral or tube feeding), formula profile used in intervention and in control group (brand name, percentage of TE from fat and MUFAs, type of carbohydrates) and outcome addressed (Table 1).

The quality methodology of the included studies was evaluated according to the Jadad scale for RCTs and is provided in Table 1. A prospectively developed protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42018108931). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in the reporting of this systematic review.[16]

Data synthesis and analysis

For the efficacy analysis, means and standard deviations (SD) were collected, or determined from the standard error (SE) or confidence intervals (CIs) of each intervention group. For the evaluation of continuous measurements, the standardised mean difference (SMD) was established as an analysis model because the heterogeneity of the studies in several aspects (the units of measurement, times of determination of the variables, duration of exposure to enteral formula or even fat differences in the composition of the EN formula). In this way, effect sizes for continuous outcome data were calculated as SMD because selected studies used different assessment tools for the same construct, with 95% CI, using the inverse variance test. SMD effect sizes of <0.4 were considered low, 0.4-0.7 moderate, and >0.7 high.[1] We considered the statistical significance when the CI of that effect size did not cross the zero-neutral value.

For the safety ~~study~~, where the variable studied was dichotomic (adverse event), the effect of the treatment was quantified through the odds ratio (OR) providing a final joint measurement, as in continuous variables, which gives the effect size found. The heterogeneity between studies was statistically studied through the chi-square test and I^2 index. An I^2 value < 25% was considered to represent low heterogeneity and >75% represented high heterogeneity.[18]

We used a random effects model when the heterogeneity found was statistically significant ($p < 0.05$). When no statistical significance was found in the heterogeneity test, a fixed effects model was selected. It was not possible to determine the risk of publication bias from funnel plot graphs for each evaluated outcome due to the small number of studies included in each outcome. All analyses were done with the STATA SE 13.1 user for meta-analysis (metan) statistics program.

RESULTS

Search findings

A total of 385 studies were identified using the planned search strategy (Figure 1). From them, 380 were screened after duplicates were removed. After reading titles and abstracts, 346 were excluded, and 34 full texts were selected to be assessed for eligibility. From them, a total of 16 articles were excluded due to type of design (not an RCT) or intervention (formula in the intervention group did not contain ≥ 20%

of the TE from MUFA or ≥ 40% of TE from fat). Finally, 18 studies met the inclusion criteria and were included into the systematic review and meta-analysis (Figure 1). Data from included studies were divided into postprandial response and MLFU studies. We identified 6 studies with available postprandial response data[19-24], 10 studies with MLFU data[27-36] and 3 studies had both postprandial response and MLFU data[20,25,26]. The characteristics of the included studies are shown in Table 1.

Postprandial data

In the eight postprandial response studies, formula was administered orally [20-25], except in two of the studies, in which it was provided as a tube feed [19,26]. With regard to hypoglycaemic treatment, patients with DM were treated with oral antidiabetic drugs (DM-oa)[19,20,22-25], except in two studies,[21,26] in which some patients received insulin (DM-i). In one postprandial response study, authors showed the results separately[21]. In the other study,[26] half of the patients needed insulin and the other half required oral antidiabetic drugs, but results were shown globally. None of the studies included patients with stress-induced hyperglycaemia. All studies shared the same methodology, where patients consumed the nutritional formula instead of breakfast along with the hypoglycaemic treatment, and then the postprandial glucose and insulin response was measured. DSF was administrated as a tube feed only in two studies[19,26].

In all studies, DSFs provided ≥ 20% of the TE from MUFAs. But, their compositions were not homogeneous (range, 26.1[26] - 35.7%[21]). Regarding the contribution of total fats, all contribute ≥ 40% of TE, except one that contributes 38%[26], although it meets the criteria of ≥ 20% of the TE from MUFAs. The STDFs used in the studies as a control formula were quite heterogeneous in their fat composition. They contribute between 19.4[19] and 7.9%[25] of the total caloric intake in the form of MUFAs and between 34.4[19] and 29%[20,23] of total fats. This means that the differences in the total caloric percentage corresponding to total fat between the DSFs and the STDFs used in the different studies vary from 19% to 20%[21-25], 16%[20], 12%[19] and 8%[26] (Table 1).

For the outcome of peak postprandial glucose response, data were provided by four studies,[20, 22,26] showing a statistically significant result in favour of the DSF group (p=0.001) with a high effect size by SMD. Although, a significant heterogeneity was observed in the analysis (I^2= 84.1%) that may hinder interpretation of the obtained effect size (SMD -1.53, 95%CI -2.44 to -0.61). However, and despite this high heterogeneity, all individual studies reported significant results favouring DSF use. Incremental glucose response data were also obtained from four studies[19,21,25,26], which showed a combined SMD of -1.19 (95% CI -1.71 to -0.68), which is statistically significant (p<0.001), and high effect size, with lower heterogeneity (I^2=58.3%). Likewise, a statistically significant result was also observed when analysing the

area under the curve of plasma insulin (iAUC) provided by three studies[19,20,24] (p=0.01), without significant heterogeneity (p=0.888), but moderate effect size by SMD (SMD -0.65, CI -1.03 to -0.27) (Table 2 and Figure 2).

Data from medium- /long-term follow-up studies

In the 13 MLFU studies[20,25-36], there were patients with different hyperglycaemic situations: with only DM-oa[19,25,35], with only DM-I[33,36], with only stress hyperglycaemia[27], a mix of DM-oa and DM-i[26,29,34], and a mix of DM-oa, DM-i and stress hyperglycaemia[28,30-32]. The route of administration in all MLFU studies was continuous tube feed[26-34,36], except for two[25,35]. The differences in total fat content between the DSFs and the STDFs was 26 %[31], 19% to 20%[25,29,32,34,35], 15% to 16%[19,33,36], 10% to 11%[28,30,32], 8%[26] and 4.5%[27] (Table 1). Table 3 and Figure 3 show the effect sizes observed for metabolic outcome measures in included studies.

Mean blood glucose data were obtained from eight studies[19,27-32,34] and were pooled in a meta-analysis. They provided a statistically significant and moderate effect size in favour of DSF use (SMD -0.41, 95% CI -0.63 to -0.19) without significant inter-study heterogeneity. The change from baseline was calculated between DSF and STDF arms for HbA1c levels in five studies that had analysable data[25,26,33,34,36] showing an SMD of -0.63 (95% CI -1.21 to -0.05), resulting into a moderately favourable effect for the DSF arm, but with significant heterogeneity (0.007). For GV[20,27,28,32], there was a high effect in favour of the DSF group showing an SMD of -0.93 (95%CI -1.55 to -0.31), but again, with significant heterogeneity (0.002). With regard to the mean insulin dose required, analysable data were obtained from five studies,[20,30-32] which showed a moderate effect size in favour of the DSF group with an SMD -0.49 (95%CI -0.85 to -0.14). However, again, significant inter-study heterogeneity was found (p=0.02), meaning that CIs may actually be wider due to the effect of the random model used. Six studies[25,29,30-32,34] were analysed providing blood triglycerides (TG) levels. They showed statistically significant but low effect size of SMD -0.34 (95%CI -0.65 -0.03) and inter-study homogeneity (p=0.42). Mean blood HDL data were obtained from six studies[25,26,29-31,34] reporting a SMD of 0.42 (95% CI 0.08 to 0.7), which resulted in a significantly higher moderate level of HDL associated with DSF use with inter-study homogeneity (p=0.075). In relation to safety and tolerance, gastrointestinal adverse events reported by the authors of the included studies were analysed[20,23,28-30,32,33,35,36], without showing significant differences between treatments.

DISCUSSION

The present systematic review and meta-analysis provides evidence on the efficacy of high MUFA DSF use versus STDF in patients with DM. Most of analysed outcomes showed a significant and positive

effect size in favour of DSF both in postprandial response and MLFU studies. Non-significant differences were observed regarding adverse events. Our results are in agreement with recently published reviews, which reported health benefits associated with the use of DSFs high in MUFAs and low in carbohydrate levels in patients with DM.[37,38]

There is no consensus about the optimal composition of DSFs. Newer formulas have replaced part of their carbohydrates by MUFAs up to 35% of TE and included dietary fibres.[14] Another common characteristic of DSFs is the presence of low glycaemic index (GI) carbohydrates.[13] Our inclusion criteria considered high MUFA DSFs those formulas containing at least 20 % of TE from MUFAs or at least 40% from total fat, according to the definition provided by the ESPEN guidelines.[14] The main strength of this meta-analysis is the high number of studies included, which may help define the minimum amount of MUFAs that a DSF may contain to provide improved health outcomes in patients with DM. To our knowledge, this is the first systematic review and meta-analysis that aims to assess the role of high MUFA and fat content in DSFs as compared to STDFs.

Hyperglycaemia has been related to poor metabolic outcomes in patients using enteral feeding[4]. Several guidelines have proposed cut-off levels of HbA1c < 7% and a fasting and postprandial capillary plasma glucose between 80 and 130 mg/dL and < 180 mg/dL, respectively, for DM control both in general wards and critical care units.[39-41] In our study, the postprandial glycaemic response (postprandial and incremental peak) was lower using high MUFA DSFs as compared to STDFs. These data were consistent through all studies included in the meta-analysis, but also in those that were not included in the pooled analysis due to lack of accurate quantitative data.[24,35] This is in agreement with findings observed by a previous meta-analysis, which also showed that DSFs had significantly lower postprandial increase in blood glucose concentrations compared with STDFs[10].

Mean blood glucose level was significantly lower in the high MUFA DSF groups in most of MLFU studies included, which was also associated with a homogeneous effect size. On the other hand, when the fasting blood glucose was reported as a change from baseline, and as compared to STDFs, a significantly decreased change was observed with DSFs, although with a certain level of inter-study heterogeneity. HbA1 levels were improved after high MUFA DSF use in our pooled analysis, but this effect was not consistent in all the included studies. The review by Elia et al.[10] found similar results and also discussed this discrepancy.

Two studies not included in our pooled analysis did not show differences either in the change or in the absolute levels of HbA1c when comparing high MUFA DSFs and STDFs[29,35]. We could argue that minimum intervention duration is required to observe such differences among these parameters.

Results related to an improvement in postprandial glucose response with high MUFA DSF use were consistent in included studies, but not those related to fasting glucose levels. The relative contribution of postprandial or fasting glucose to the HbA1c level has been discussed largely. Both fasting and postprandial glycaemia contribute to HbA1c, but the contribution of the post-meal glucose response is greater as the HbA1c level gets closer to 7%[41]. It must be pointed out that a high rate of dropouts was described in included studies, and HbA1c level was usually addressed as a secondary endpoint. Therefore, it is possible that observed results could have been underpowered to detect differences between treatments.

Increased GV in acute patients has been related to poor health outcomes in some observational studies[42]. Some authors concluded that reducing GV is an important health outcome in hospitalised non-critical and critical patients,[32,43] particularly in subjects with stress hyperglycaemia.[43] We found an important effect size favouring the use of the DSFs in DM patients for this outcome. To our knowledge, no other meta-analysis has reported this finding before.

In our pooled analysis, the daily insulin dose required to maintain the glucose target level was found to be lower with DSFs. The meta-analysis by Elia et al.[10] did not include this outcome, although individual studies including this outcome were described, which were pointing to a diminished need of insulin therapy related to DSF use. These results are of high clinical relevance since frailty is a common comorbidity in patients with DM, and treatment simplicity is always advisable.[44] In addition, this is an important health concern considering that hypoglycaemia is associated with increased complications as well as higher risk of mortality, mainly in critical patients[45].

On the other hand, included studies reported a decrease in mean blood TG and increased HDL cholesterol levels associated with high MUFA DSF treatment. These were secondary endpoints addressed in the individual included studies, and the power to detect differences was expected to be low. However, these findings have biological plausibility. DM ~~type 2~~ and stress hyperglycaemia are related to insulin resistance, which has been linked to an increase in TG secretion[46]. Plasma insulin after DSF treatment was found to be lower when compared to STDFs, which explains, in part, the effect on TG levels. On the other hand, levels of HDL cholesterol increased after DSF use. It is known that exchange processes between TG-rich lipoproteins and HDL result in the formation of TG-rich HDL, which has a short half-life[47].

Perhaps, the relevance of the plasma lipid changes must be analysed in a longer-term period. An observational study describing the effectiveness of a DSF to treat undernutrition in elderly patients also observed an increase in the levels of total, LDL-, and HDL-cholesterol from baseline, while an

improvement in the nutritional status was described.[48] The observed reverse epidemiological effect of typical cardiovascular risk factors for mortality in the elderly and under chronic disease must be considered when the effect of DSFs on lipids levels is discussed[49]

One of the main limitations of the current study is that we focused on the contribution MUFAs and fats, without considering other important components of DSFs such as slow-digestion carbohydrates and fibre. The type of carbohydrates included in DSFs has been changing over the past years, and we were unable to group the studies according to these criteria, mainly due to high heterogeneity found in formula composition used in included studies. Although the quantity and quality of carbohydrate content in an ONS have been demonstrated to have a major role in blood glucose management[38], this is still a quite controversial topic. A clinical study compared two formulas only differing in carbohydrate composition and reported that the use of unmodified maltodextrins had no clear advantages over sucrose on the postprandial glucose response in healthy individuals as well as in patients with type 2 DM[50]. Other studies suggested that both quantity and quality of carbohydrates contribute to the postprandial glycaemic response,[51] or even found a lower glucose AUC for a formula containing low glycaemic index carbohydrates as compared with other with maltodextrins, although without significant differences[52]. Another limitation of our study is the high heterogeneity of our results. This has forced us to present the differences with an indirect measure such as SMD. It would have been more interesting to present the results with clinically applicable units of measure. This heterogeneity of the results does not allow us to consider the effect size observed in all its intensity. Despite this heterogenicity, the results of the postprandial response studies show a moderate-large effect size and small-moderate effect in MLFU studies according to SMD with an always positive level of significance in favour of the high-MUFA DSFs.

High-quality trials adequately powered for these clinical outcomes are needed to assess efficacy of DSFs. Clinical trials to achieve these objectives should include an adequate number of patients, with lower dropout rates, longer duration, and preferably with a double-blind design. It is important that patients of each study are homogeneous in pancreatic insulin reserve, weight, pathology that indicates ~~enteral nutrition~~ and route of administration. It would be also important to avoid including different groups of patients with type 1 and 2 DM and stress-induced hyperglycaemia, previously treated with oral antidiabetics or insulin. Route of administration criteria such as oral or tube feeding, continuous or intermittent, during hospitalisation for an acute process, at home or in patients admitted to centres for chronic diseases should be carefully considered as well[13].

In conclusion, our meta-analysis provides consistent evidence that DSFs containing 20% or more energy from MUFAs or 40% or more energy from fat have beneficial effects on peak postprandial glucose, incremental glucose response and glucose variability among individuals with DM or stress hyperglycaemia as compared with STDFs.

REFERENCES

1. Thomson, A., *The enteral vs parenteral nutrition debate revisited.* JPEN J Parenter Enteral Nutr, 2008;**32**:474-81. doi: 10.1177/0148607108316192
2. Oliveira Fuster G, García García-Doncel L, Carral SanLaureano F, Domenech Cienfuegos I, Arencibia Rivero T, Manzano Martín MV. *Dietary-therapeutic product supply in unitary doses at a university hospital: effect on consumption and costs.* Nutr Hosp, 2000;**15**:58-63.
3. Dorner B, Posthauer ME, Friedrich EK, Robinson GE. *Enteral nutrition for older adults in nursing facilities.* Nutr Clin Pract, 2011;**26**:261-72. doi:10.1177/0884533611405794
4. Pancorbo-Hidalgo, P.L., F.P. Garcia-Fernandez, and C. Ramirez-Perez, *Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit.* J Clin Nurs, 2001;**10**:482-90.
5. Arinzon Z, Shabat S, Shuval I, Peisakh A, Berner Y. *Prevalence of diabetes mellitus in elderly patients received enteral nutrition long-term care service.* Arch Gerontol Geriatr, 2008;**47**:383-93. doi: 10.1016/j.archger.2007.09.001
6. Sanz-Paris A, Boj-Carceller D, Lardies-Sanchez B, Perez-Fernandez L, Cruz-Jentoft AJ. *Health-Care Costs, Glycemic Control and Nutritional Status in Malnourished Older Diabetics Treated with a Hypercaloric Diabetes-Specific Enteral Nutritional Formula*. Nutrients. 2016 Mar 9;**8**(3):153. DOI: 10.3390/nu8030153.
7. McMahon MM, Nystrom E, Braunschweig C, Miles J, Compher C; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors; American Society for Parenteral and Enteral Nutrition. *A.S.P.E.N. clinical guidelines: nutrition support of adult patients with hyperglycemia.* JPEN J Parenter Enteral Nutr, 2013;**37**:23-36. DOI: 10.1177/0148607112452001
8. Barazzoni R, Deutz NEP, Biolo G, Bischoff S, Boirie Y, Cederholm T, Cuerda C, Delzenne N, Leon Sanz M, Ljungqvist O, Muscaritoli M, Pichard C, Preiser JC, Sbraccia P, Singer P, Tappy L, Thorens B, Van Gossum A, Vettor R, Calder PC. *Carbohydrates and insulin resistance in clinical nutrition:*

Recommendations from the ESPEN expert group. Clin Nutr, 2017;**36**:355-363. DOI: 10.1016/j.clnu.2016.09.010

9. American Diabetes Association. *15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2019.* Diabetes Care. 2019 Jan;42(Suppl 1):S173-S181. doi: 10.2337/dc19-S015.
10. Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ. *Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis.* Diabetes Care, 2005;**28**:2267-79. DOI: 10.2337/diacare.28.9.2267
11. Olveira G, García-Luna PP, Pereira JL, Rebollo I, García-Almeida JM, Serrano P, Irles JA, Muñoz-Aguilar A, Molina MJ, Tapia MJ; GARIN Group Andalusian Group for Nutrition Reflection and Investigation. *Recommendations of the GARIN group for managing non-critically ill patients with diabetes or stress hyperglycaemia and artificial nutrition.* Nutr Hosp, 2012;**27:**1837-49. DOI: 10.3305/nh.2012.27.6.6076
12. Ojo, O. and J. Brooke, *Evaluation of the role of enteral nutrition in managing patients with diabetes: a systematic review.* Nutrients, 2014;**6**:5142-52. DOI: 10.3390/nu6115142
13. Sanz-Paris A, Álvarez Hernández J, Ballesteros-Pomar MD, Botella-Romero F, León-Sanz M, Martín-Palmero Á, Martínez Olmos MÁ, Olveira G. *Evidence-based recommendations and expert consensus on enteral nutrition in the adult patient with diabetes mellitus or hyperglycemia.* Nutrition, 2017;**41**:58-67. DOI: 10.1016/j.nut.2017.02.014.
14. Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, Schneider S, van den Berghe G, Pichard C. *Introductory to the ESPEN Guidelines on Enteral Nutrition: Terminology, definitions and general topics.* Clin Nutr, 2006;**25**:180-6. DOI: 10.1016/j.clnu.2006.02.007
15. Jadad AR, Enkin M. Randomized controlled trials. Questions, answers and musings (2ª ed). Blackwell; 2007.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. J Clin Epidemiol. 2009;62(10):1006–12.
17. Higgins Julian, Green. 17.8.2 Study summaries using more than one patient reported outcome. In: Cochrane handbook for systematic reviews of interventions; 2011.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.
19. Lansink M, Hofman Z, Genovese S, Rouws CHFC, Ceriello A. Improved Glucose Profile in Patients With Type 2 Diabetes With a New, High-Protein, Diabetes-Specific Tube Feed During 4 Hours of

409 Continuous Feeding. JPEN J Parenter Enteral Nutr. 2017;41:968-75. DOI:
410 10.1177/0148607115625635
411 20. Alish CJ, Garvey WT, Maki KC, Sacks GS, Hustead DS, Hegazi RA, Mustad VA. A diabetes-specific
412 enteral formula improves glycemic variability in patients with type 2 diabetes. Diabetes Technol
413 Ther. 2010;12:419-25. DOI: 10.1089/dia.2009.0185
414 21. Sanz-París A, Calvo L, Guallard A, Salazar I, Albero R. High-fat versus high-carbohydrate enteral
415 formulae: effect on blood glucose, C-peptide, and ketones in patients with type 2 diabetes
416 treated with insulin or sulfonylurea. Nutrition, 1998;14:840-5.
417 22. Vanschoonbeek K, Lansink M, van Laere KM, Senden JM, Verdijk LB, van Loon LJ1. Slowly
418 digestible carbohydrate sources can be used to attenuate the postprandial glycemic response to
419 the ingestion of diabetes-specific enteral formulas. Diabetes Educ. 2009;35:631-40. DOI:
420 10.1177/0145721709335466
421 23. Voss AC, Maki KC, Garvey WT, Hustead DS, Alish C, Fix B, Mustad VA. Effect of two
422 carbohydrate-modified tube-feeding formulas on metabolic responses in patients with type 2
423 diabetes. Nutrition. 2008;24:990-7. DOI: 10.1016/j.nut.2008.06.009
424 24. Yokoyama J, Someya Y, Yoshihara R, Ishii H. Effects of high-monounsaturated fatty acid enteral
425 formula versus high-carbohydrate enteral formula on plasma glucose concentration and insulin
426 secretion in healthy individuals and diabetic patients. J Int Med Res. 2008;36:137-46. DOI:
427 10.1177/147323000803600117
428 25. McCargar LJ, Innis SM, Bowron E, Leichter J, Dawson K, Toth E, Wall K. Effect of enteral
429 nutritional products differing in carbohydrate and fat on indices of carbohydrate and lipid
430 metabolism in patients with NIDDM. Mol Cell Biochem. 1998;188:81-9.
431 26. Vaisman N, Lansink M, Rouws CH, van Laere KM, Segal R, Niv E, Bowling TE, Waitzberg DL,
432 Morley JE. Tube feeding with a diabetes-specific feed for 12 weeks improves glycaemic control
433 in type 2 diabetes patients. Clin Nutr. 2009;28:549-55. DOI: 10.1016/j.clnu.2009.05.004
434 27. Egi M, Toda Y, Katayama H, Yokoyama M, Morita K, Arai H, Yamatsuji T, Bailey M, Naomoto Y.
435 Safer glycemic control using isomaltulose-based enteral formula: a pilot randomized crossover
436 trial. J Crit Care. 2010;25:90-6. DOI: 10.1016/j.jcrc.2009.07.006
437 28. van Steen SC, Rijkenberg S, Sechterberger MK, DeVries JH, van der Voort PHJ. Glycemic Effects
438 of a Low-Carbohydrate Enteral Formula Compared With an Enteral Formula of Standard

Composition in Critically Ill Patients: An Open-Label Randomized Controlled Clinical Trial. Journal of Parenteral and Enteral Nutrition. 2018;6:1035-1045. DOI: 10.1002/jpen.1045

29. León-Sanz M, García-Luna PP, Sanz-París A, Gómez-Candela C, Casimiro C, Chamorro J, Pereira-Cunill JL, Martin-Palmero A, Trallero R, Martínez J, Ordóñez FJ, García-Peris P, Camarero E, Gómez-Enterría P, Cabrerizo L, Perez-de-la-Cruz A, Sánchez C, García-de-Lorenzo A, Rodríguez N, Usán L; Abbott SPAI-97-004 Study Cooperative Group. Glycemic and lipid control in hospitalized type 2 diabetic patients: evaluation of 2 enteral nutrition formulas (low carbohydrate-high monounsaturated fat vs high carbohydrate). JPEN J Parenter Enteral Nutr. 2005;29:21-9.

30. Mesejo A, Acosta JA, Ortega C, Vila J, Fernández M, Ferreres J, Sanchis JC, López F. Comparison of a high-protein disease-specific enteral formula with a high-protein enteral formula in hyperglycemic critically ill patients. Clin Nutr. 2003;22:295-305.

31. Celaya S, Sanz A, Homs C, Luque P, de la Orden P, Civeira E, Elósegui LM. Experience with an enteral diet with fiber and a high fat content in ICU patients with glucose intolerance. Nutr Hosp. 1992;7:260-9.

32. Mesejo A, Montejo-González JC, Vaquerizo-Alonso C, Lobo-Tamer G, Zabarte-Martinez M, Herrero-Meseguer JI, Acosta-Escribano J, Blesa-Malpica A, Martinez-Lozano F. Diabetes-specific enteral nutrition formula in hyperglycemic, mechanically ventilated, critically ill patients: a prospective, open-label, blind-randomized, multicenter study. Crit Care. 2015;19:390. DOI: 10.1186/s13054-015-1108-1

33. Pohl M, Mayr P, Mertl-Roetzer M, Lauster F, Haslbeck M, Hipper B, Steube D, Tietjen M, Eriksen J, Rahlfs VW. Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: Stage II of a randomized, controlled multicenter trial. Journal of Parenteral and Enteral Nutrition 2009 33:1 (37-49). DOI: 10.1177/0148607108324582

34. Craig LD, Nicholson S, SilVerstone FA, Kennedy RD. Use of a reduced-carbohydrate, modified-fat enteral formula for improving metabolic control and clinical outcomes in long-term care residents with type 2 diabetes: results of a pilot trial. Nutrition. 1998;14:529-34

35. Magnoni D, Rouws CH, Lansink M, van Laere KM, Campos AC. Long-term use of a diabetes-specific oral nutritional supplement results in a low-postprandial glucose response in diabetes patients. Diabetes Res Clin Pract. 2008;80:75-82. DOI: 10.1016/j.diabres.2007.10.027

36. Pohl M, Mayr P, Mertl-Roetzer M, Lauster F, Lerch M, Eriksen J, Haslbeck M, Rahlfs VW. Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. Eur J Clin Nutr. 2005;59:1221-32. DOI: 10.1038/sj.ejcn.1602232
37. Qian F, Korat AA, Malik V, Hu FB. Metabolic Effects of Monounsaturated Fatty Acid-Enriched Diets Compared With Carbohydrate or Polyunsaturated Fatty Acid-Enriched Diets in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Diabetes Care. 2016;39:1448-57. DOI: 10.2337/dc16-0513.
38. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract, 2017;131:124-131. DOI: 10.1016/j.diabres.2017.07.006
39. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. *Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.).* JPEN J Parenter Enteral Nutr, 2016:40:159-211. doi: 10.1177/0148607115621863
40. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, Preiser JC, van Zanten ARH, Oczkowski S, Szczeklik W, Bischoff SC. *ESPEN guideline on clinical nutrition in the intensive care unit.* Clin Nutr, 2019;38:48-79. DOI: 10.1016/j.clnu.2018.08.037
41. American Diabetes Association. *6. Glycemic Targets: Standards of Medical Care in Diabetes-2019.* Jan;42(Suppl 1):S61-S70. DOI: 10.2337/dc19-S006. Review.
42. Akirov A, Diker-Cohen T, Masri-Iraqi H, Shimon I. *High Glucose Variability Increases Mortality Risk in Hospitalized Patients.* J Clin Endocrinol Metab, 2017;**102**:2230-2241. DOI: 10.1210/jc.2017-00450.
43. Krinsley JS, Maurer P, Holewinski S, Hayes R, McComsey D, Umpierrez GE, Nasraway SA. *Glucose Control, Diabetes Status, and Mortality in Critically Ill Patients: The Continuum From Intensive Care Unit Admission to Hospital Discharge.* Mayo Clin Proc, 2017;92:1019-1029. DOI: 10.1016/j.mayocp.2017.04.015
44. American Diabetes Association. *12. Older Adults: Standards of Medical Care in Diabetes-2019.* Diabetes Care, 2019;42(Suppl 1):139-147. DOI: 10.2337/dc19-S012.

45. Hermanides J, Bosman RJ, Vriesendorp TM, Dotsch R, Rosendaal FR, Zandstra DF, Hoekstra JB, DeVries JH. *Hypoglycemia is associated with intensive care unit mortality.* Crit Care Med, 2010,38:1430-4. DOI: 10.1097/CCM.0b013e3181de562c.
46. Hirano, T., *Pathophysiology of Diabetic Dyslipidemia.* J Atheroscler Thromb, 2018;25:771-82. DOI: 10.5551/jat.RV17023
47. Guerin M, Egger P, Soudant C, Le Goff W, van Tol A, Dupuis R, Chapman MJ. *Cholesteryl ester flux from HDL to VLDL-1 is preferentially enhanced in type IIB hyperlipidemia in the postprandial state.* J Lipid Res, 2002;**43**:1652-60. DOI: 10.1194/jlr.m200135-jlr200
48. Matia Martin P, Robles Agudo F, Lopez Medina JA, Sanz Paris A, Tarazona Santabalbina F, Domenech Pascual JR, Lopez Penabad L, Sanz Barriuso R; GluceNut Study Group. Effectiveness of an oral diabetes-specific supplement on nutritional status, metabolic control, quality or life, and functional status in elderly patients. A multicentre study. Clin Nutr. 2019 Jun;38(3):1253-61. DOI: 10.1016/j.clnu.2018.05.007
49. Curcio F, Sasso G, Liguori I, Ferro G, Russo G, Cellurale M, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D, Abete P. *The reverse metabolic syndrome in the elderly: Is it a "catabolic" syndrome?* Aging Clin Exp Res, 2018;30:547-54. DOI: 10.1007/s40520-017-0815-7
50. Hofman Z, van Drunen JD, de Later C, Kuipers H. *The effect of different nutritional feeds on the postprandial glucose response in healthy volunteers and patients with type II diabetes.* Eur J Clin Nutr, 2004;58:1553-6. DOI: 10.1038/sj.ejcn.1602007
51. Devitt C, McKenzie K, More SJ, Heanue K, McCoy F. *Opportunities and constraints to improving milk quality in Ireland: enabling change through collective action.* J Dairy Sci, 2013;96:2661-70. DOI: 10.3168/jds.2012-6001
52. Lissé Angarita Dávila, J.L.M., Daniel Aparicio Camargo, Karla Parra Zuleta, María Uzcátegui González, and S.D.A.y.N.R.V. Virginia Céspedes Nava. Glycemic index, glycemic load and insulin response of two formulas of isoglucose with different sweeteners and dietary fiber in healthy adults and type-2 diabetes. Nutr Hosp. 2017 Jun 5;34(3):532-9. DOI: 10.20960/nh.654.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis (n = 18).

						Sample size			DSF composition			STDF compostion			Difference in % of energy from	
	Study design	Jadad score	Arms	Duration of intervention	Route of administration	DM-oa	DM-i	SH	Fat (% TE)	MUFA (% TE)	Carbohydrate type	Fat (% TE)	MUFA (% TE)	Carbohydrate type	Fat	MUFA
Lansink 2017[19]	Crossover, RCT	5	2	Postprandial	Nasogastric tube	24	-	-	46.4	27.6	**Nutrison Advanced Diason Energy HP** Isomaltulose	34,4	19.4	**Nutrison Energy Multi Fibre** Sugars, polysaccharides	12	8.2
Alish 2010[20]	Parallel, RCT	2	2	Postprandial	Oral	18	-	-	45	27.7	**Glucerna 1.2** Maltodextrin, isomaltulose, sucromalt, fibersol, fructo-oligosaccharides, soy and oat fiber, glycerine	29	10.4	Corn maltodextrin, corn syrup solids, short-chain fructo-oligosaccharides, soy and oat fibre	16	17.3
Sanz Paris (I) 1998[21]	Parallel, RCT	1	2	Postprandial	Oral	-	40	-	50	35.7	**Glucerna 1.0** Fructose, corn maltodextrin, soy fiber	31	8.6	**Precitene Diabet**. Fructose, starch, fibre	19	27.1
Sanz Paris (A) 1998[21]	Parallel, RCT	1	2	Postprandial	Oral	12	-	-	50	35.7	**Glucerna 1.0** Fructose, corn maltodextrin, soy fiber	31	8.6	**Precitene Diabet**. Fructose, starch, fibre	19	27.1
Vanschoonbeek 2009[22]	Crossover, RCT	3	2	Postprandial	Oral	15	-	-	50	34.8	**Glucerna** Fructose, maltodextrin, fructo-oligosaccharides	30	12.6	**Isosource Fiber** Polysaccharides, fibre	20	22.2
Voss 2008[23]	Crossover, RCT	4	3	Postprandial	Oral	48	-	-	49	32	Fibersol, fructose, maltitol, short-chain fructo-oligosaccharides	29	15	Corn maltodextrin, fibre	20	17
Yokoyama 2008[24]	Crossover, RCT	1	2	Postprandial	Oral	12	-	-	49.3	34.3	**Glucerna** Maltodextrin, fructose, soy fibre	30.8	8.5	**Enrich-SF** Maltodextrin, sucrose, soluble fibre	18.5	25.8
Mc Cargar 1998[25]	Parallel, RCT	2	2	Postprandial and 28 days	Oral; 80% rec in EN	32	-	-	50	32	**Glucerna 1.0** Fructose, corn maltodextrin, soy fibre	30.5	7.9	**Ensure** Hydrolysed corn starch, sucrose	19.5	24.1

Table 1. Characteristics of the studies included in the systematic review and meta-analysis (n = 18).

Vaisman 2009[26]	Parallel, RCT	3	2	Postprandial and 12 week	Nasogastric tube	25	-	38	26.1	**Nutrison Advanced Diason**. Polysaccharides, fructose, fibre	30	18.9	Corn maltodextrin, corn syrup solids, and soy fiber	8	7.2
Egi 2010[27]	Crossover, RCT	2	2	16 hours	Jejunostomy	-	-	8	29.7	21.5	**Inslow** Dextrin, isomaltulose	25.2	12.6	Dextrin, glucose, fructose	4.5	8.9
Van Steel 2018[28]	Parallel, RCT	3	2	72 h	Nasogastric tube	18	11	72	45	29.4	**Glucerna 1.5 kcal** Maltodextrin, fibersol, oat fiber, soy fiber, fructo-oligosaccharides, isomaltulose, sucromalt, glycerine	34.8	22.8	**Fresubin Energy Fibre** Maltodextrin, sucrose, wheat dextrin, inulin	10.2	7.2
Alish 2010[19]	Crossover, RCT	1	2	5 days	Percutaneous endoscopic gastrostomy	9	-	-	45	27.7	**Glucerna 1.2** Maltodextrin, isomaltulose, sucromalt, fibersol, fructo-oligosaccharides, soy and oat fibre, glycerine	29	10.4	Corn maltodextrin, corn syrup solids, short-chain fructo-oligosaccharides and soy and oat fibre	16	17.3
Leon 2005[29]	Parallel, RCT	1	2	13 days	Nasogastric tube	104	-	50	34.2	**Glucerna 1.0** Soy polysaccharide (fiber), Corn maltodextrin, fructose	31	9.4	**Precitene Diabet**. Fructose and Starch and fibre	19	24.8
Mesejo 2003[30]	Parallel, RCT	3	2	14 days	Nasogastric tube	50		40	23.16	**Novasource Diabet Plus**. Starch and fructose and fibre	29	11.4	Sucrose and Maltodextrin without fibre	11	11.7
Celaya 1992[31]	Parallel, RCT	2	2	14 days	Nasogastric tube	3	2	30	50	35,7	**Glucerna 1.0** Maltodextrin, fructose, soy fiber	24	14.5	Maltodextrin, sucrose	26	21.2
Mesejo (a) 2015[32]	Parallel, RCT	3	3	28 days	Nasogastric tube	105		49	32,2	**Glucerna select** Modified maltodextrin, Fructose and Maltitol	30	12.9	**Isosource Protein Fibra** Standard maltodextrin and Sucrose	19	19.3
Mesejo (b) 2015[32]	Parallel, RCT	3	3	28 days	Nasogastric tube	105		40	20	**Diaba HP**. Modified maltodextrin (low dextrose equivalent and type IV resistant)	30	12.9	**Isosource Protein Fibra**. Standard maltodextrin and Sucrose	10	7.1
Pohl 2009[33]	Parallel, RCT	5	2	70 days	Nasogastric tube	-	55	-	45	32.2	**Diben** Starch, fructose, maltodextrins	30	17	Maltodextrins	15	15.2
Craig 1998[34]	Parallel, RCT	3	2	84 days	Nasogastric tube	16	18	-	50	35.7	**Glucerna.** Maltodextrin, soy polysaccharide (fibre), fructose	30	14.5	**Jevity** Maltodextrin, soy polysaccharide	20	21.2
Magnoni 2008[35]	Parallel, RCT	5	2	84 days	Oral	40	-	-	49	34.2	**Diasip** Fructose, polysaccharides, fibre	30	17.1	Sugars, polysaccharides without fibre	19	17.1
Pohl 2005[36]	Parallel, RCT	5	2	84 days	Nasogastric tube, percutaneous endoscopic	-	78	-	45	32.2	**Diben** Starch, fructose, maltodextrins	30	17	Maltodextrins	15	15.2

Table 1. Characteristics of the studies included in the systematic review and meta-analysis (n = 18).

					gastrostomy											

DM-oa, Patients with diabetes treated with oral antidiabetic; DM-i, Patients with diabetes treated with insulin; SH, Stress Hyperglycemia; TE, Total Energy; DSF, Diabetes Specific Formula; STDF, Standard Formula.

Table 2. Effect sizes for metabolic outcomes in postprandial studies[19-26]. DSF versus non-DSF in DM patients.

METABOLIC PARAMETER	Number of studies	Number of participants	SMD fixed model	CI95%	I^2	P het	P value
Peak postprandial glucose	4[20-22,26]	163	-1.53*	-2.44 to -0.61	84.1%	<0.001	<0.01
Incremental glucose response	4[19,21,25,26]	172	-1.19*	-1.71 to -0.68	58.3%	<0.05	<0.001
Plasma insulin after intake (iAUC)	3[19,20,24]	111	-0.65	-1.03 to -0.27	0.0%	0.88	<0.01

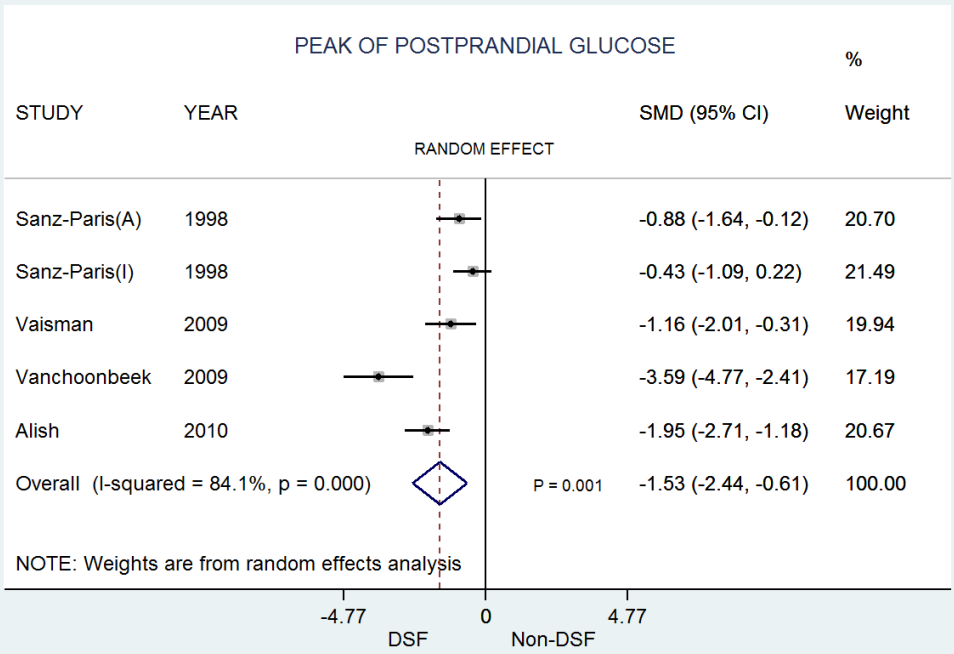
*Weights are calculated from random effects analysis. Rest is calculated using a fixed-effects model. I^2: Percentage of variance in a meta-analysis that is attributable to study heterogeneity. SMD: meta-analysis effect size by Standardized Mean Difference model (<0.4 small, 0.4-0.7 moderate and >0.7 large). CI: Confidence Interval. P het: heterogeneity p-value. AUC: area under the curve.

Table 3. Effect sizes for metabolic outcomes in medium-long term studies[20,25-36]. DSF versus STDF in DM patients.

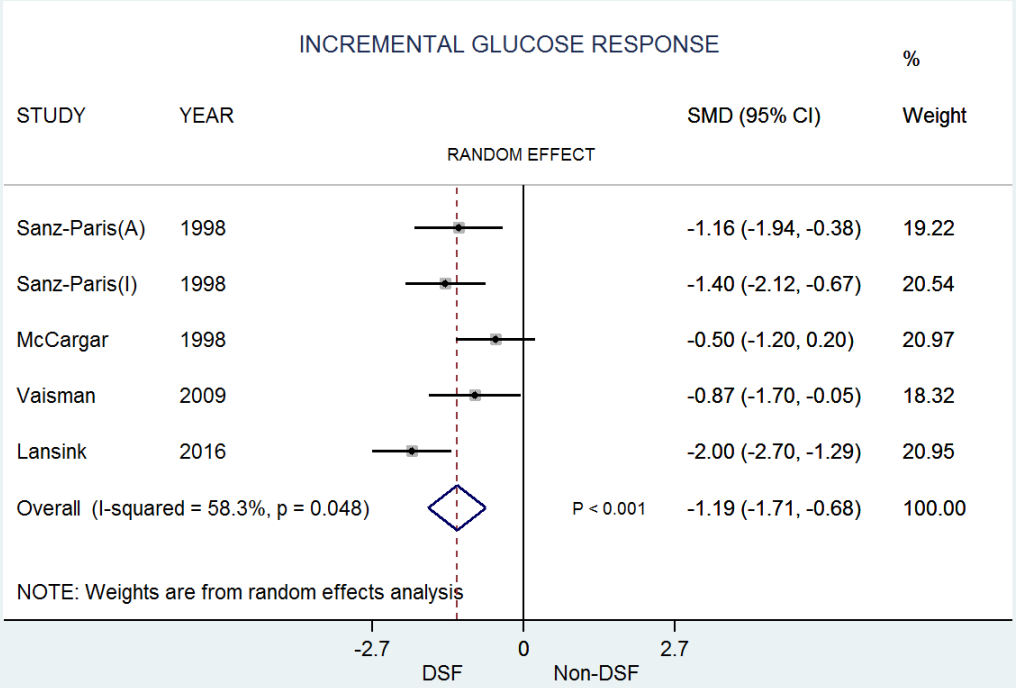
METABOLIC PARAMETER	Number of studies	Number of participants	SMD fixed model	CI95%	I^2	P het	P value
Mean blood glucose level	8[19,27-32,34]	335	-0.41	-0.63 to -0.19	31.7%	0.17	<0.001
HbA1c (change from baseline)	5[25,26,33,34,36]	186	-0.63%*	-01.21 to -0.05	71.7%	<0.01	<0.05
Glucose variability	4[20,27,28,32]	267	-0.93*	-1.55 to -0.31	76.6%	<0.01	<0.01
Mean administered insulin dose (UI/day)	4[20,30-33]	367	-0.49*	-0.85 to -0.14	68.6%	<0.05	<0.01
Mean blood triglycerides	6[25,29,30-32,34]	177	-0.34	-0.65 to -0.03	0.0%	0.42	<0.05
Mean blood high density lipoprotein (HDL)	6[25,26,29-31,34]	143	0.42	0.08 to 0.76	45.5%	0.10	<0.05
Adverse events	9[20,23,28-30,32,33,35,36]	638	OR: 0.95	0.87 to 1.05	40.6%	0.09	>0.05

*Weights are calculated from random effects analysis. Rest are calculated using a fixed-effects model. OR: Odds Ratio. I^2: Percentage of variance in a meta-analysis that is attributed to study heterogeneity. SMD: meta-analysis effect size by standardized mean difference model (<0.4 small, 0.4-0.7 moderate and >0.7 large). CI: Confidence Interval. P het: heterogeneity p-value.

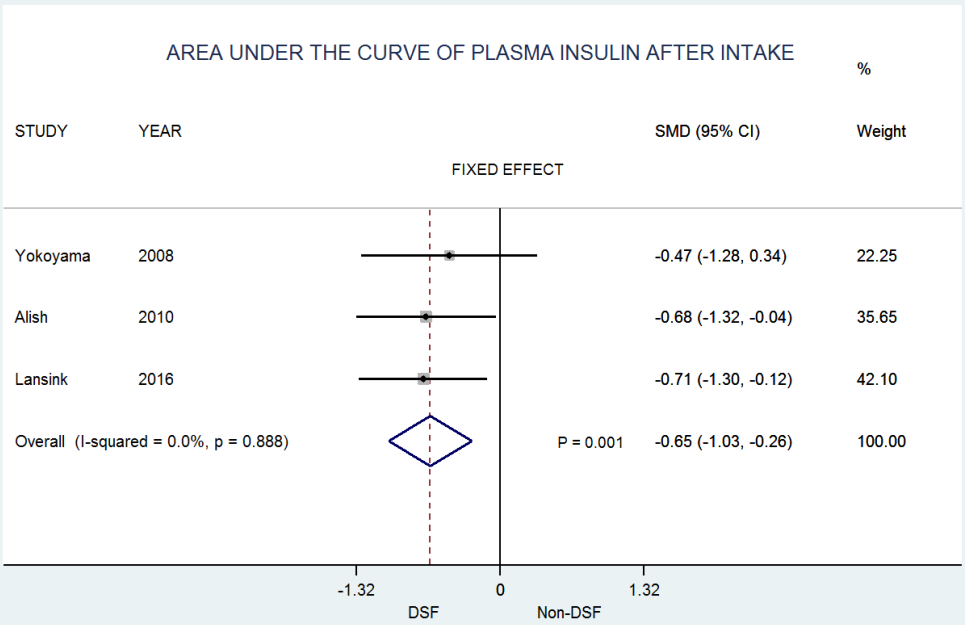
Figure 2. Forest plots analyses for metabolic outcomes in postprandial studies. DSF versus non-DSF in DM patients



Effect sizes were calculated as standardized mean differences (SMD) (<0.4 were considered small, 0.4-0.7 moderate, and >0.7 large).

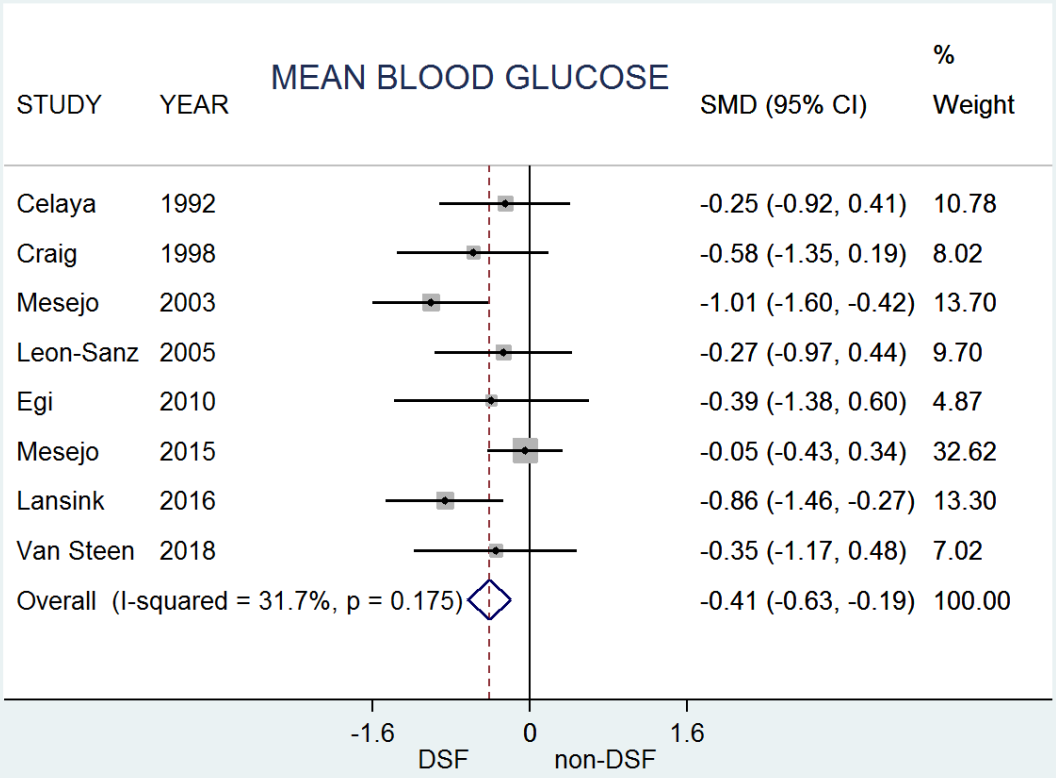


Effect sizes were calculated as standardized mean differences (SMD) (<0.4 were considered small, 0.4-0.7 moderate, and >0.7 large).



Effect sizes were calculated as standardized mean differences (SMD) (<0.4 were considered small, 0.4-0.7 moderate, and >0.7 large).

Figure 3. Forest plots analyses for metabolic outcomes in medium-long term studies. DSF versus non-DSF in DM patients



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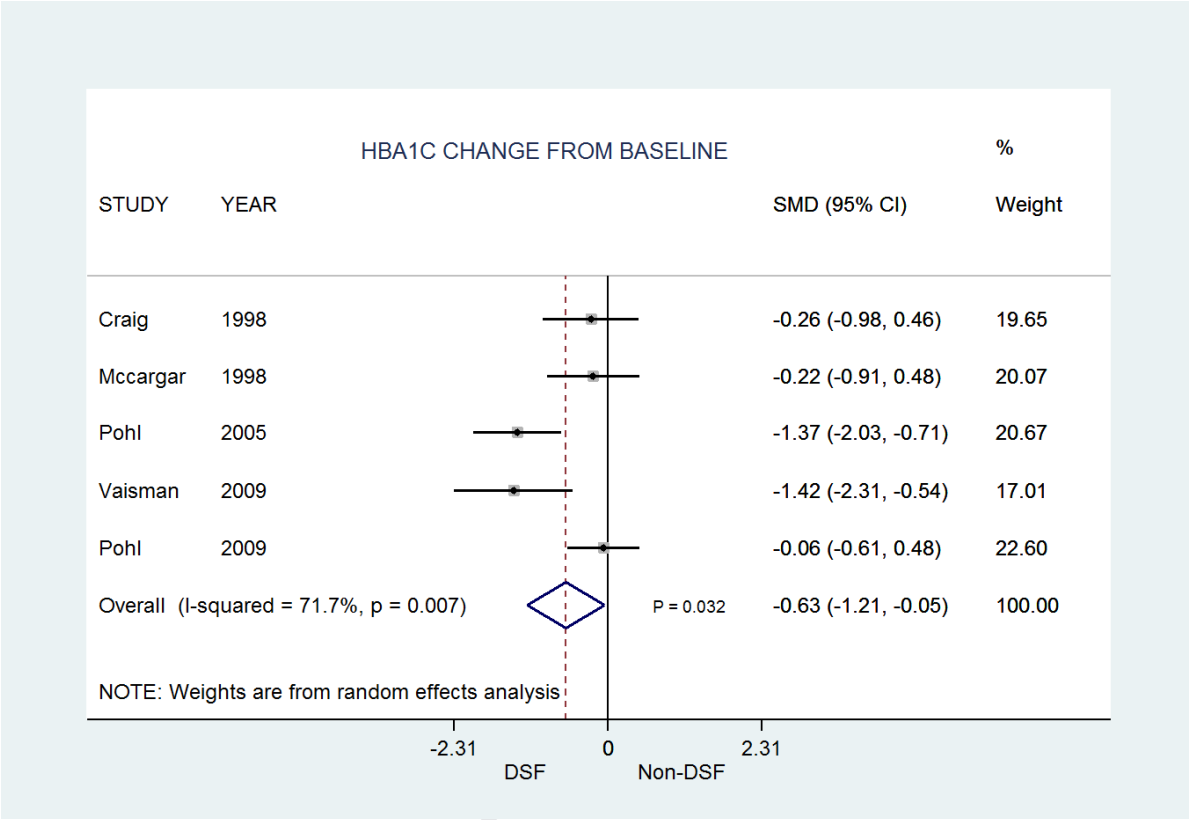

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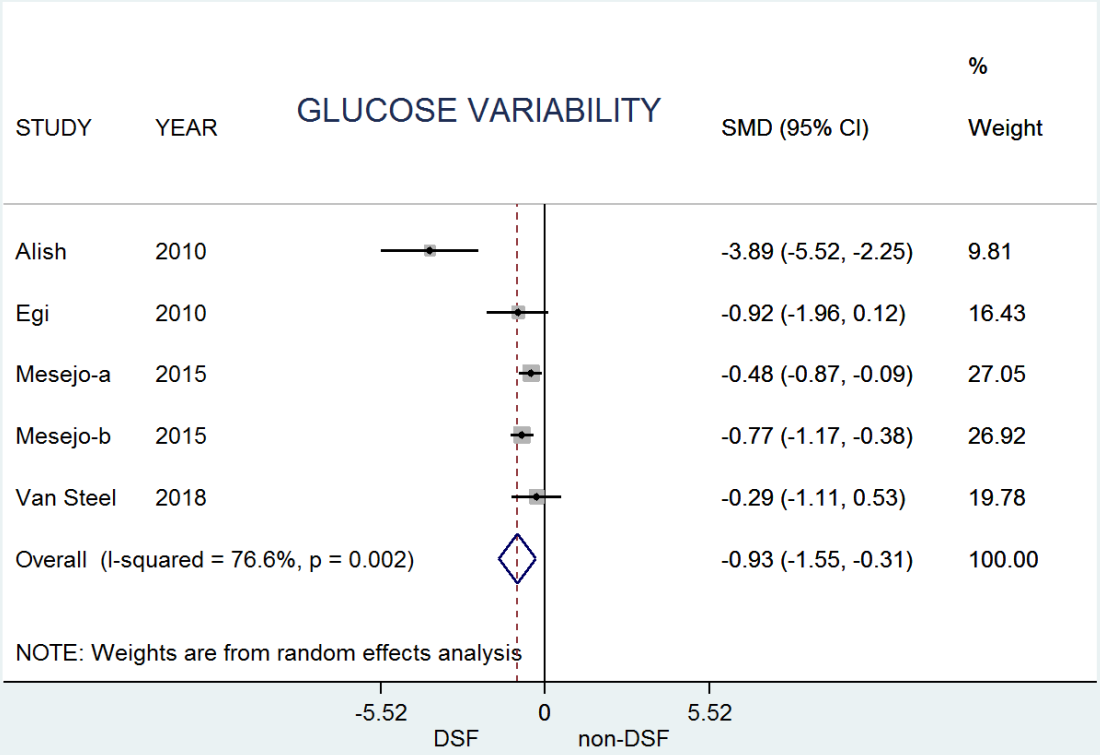

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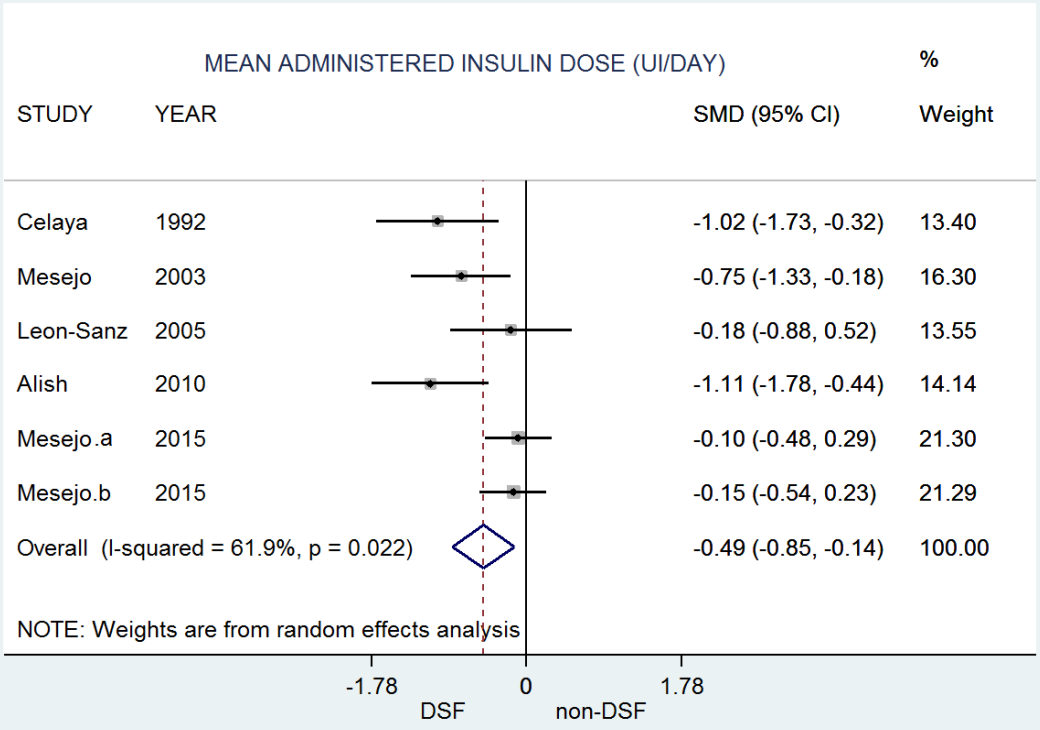
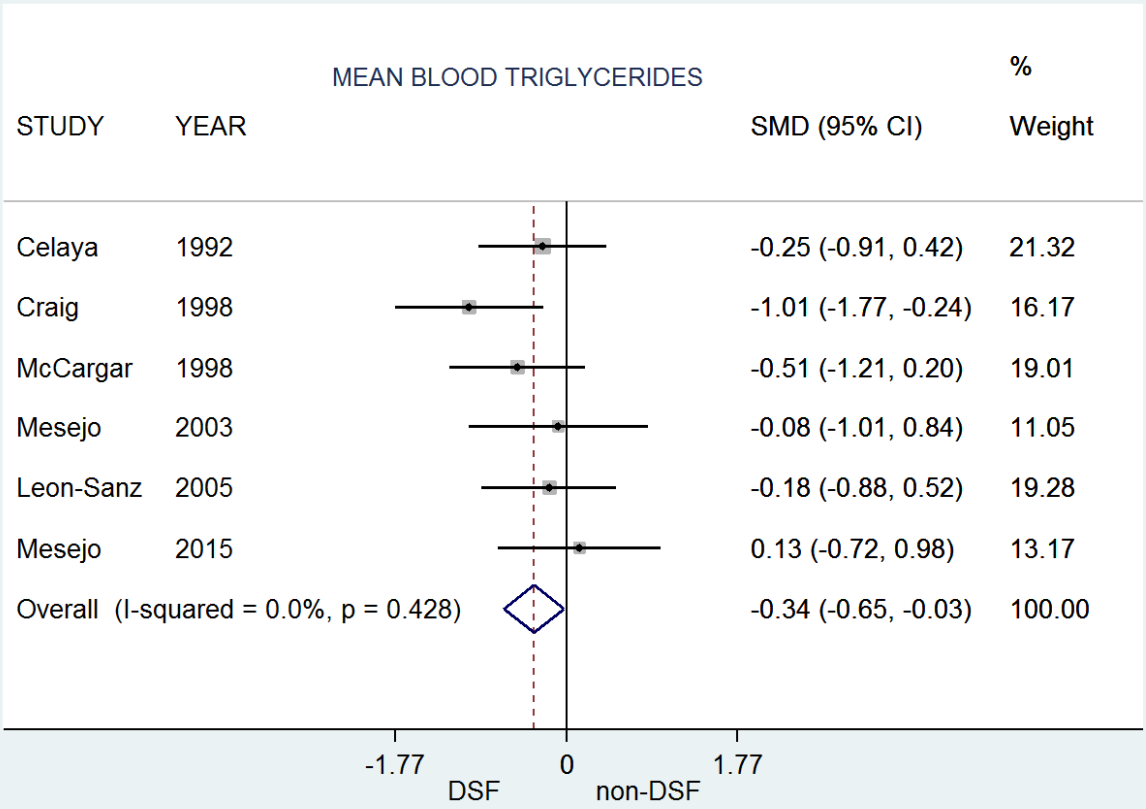


Effect sizes were calculated as standardized mean differences (SMD) (<0.4 were considered small, 0.4-0.7 moderate, and >0.7 large).



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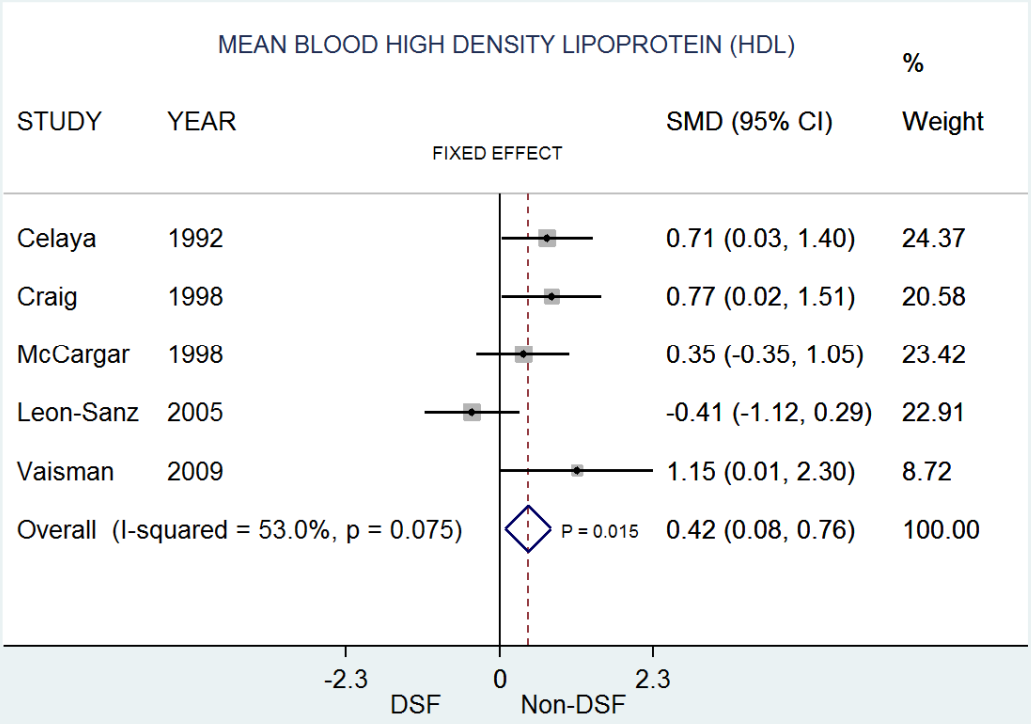

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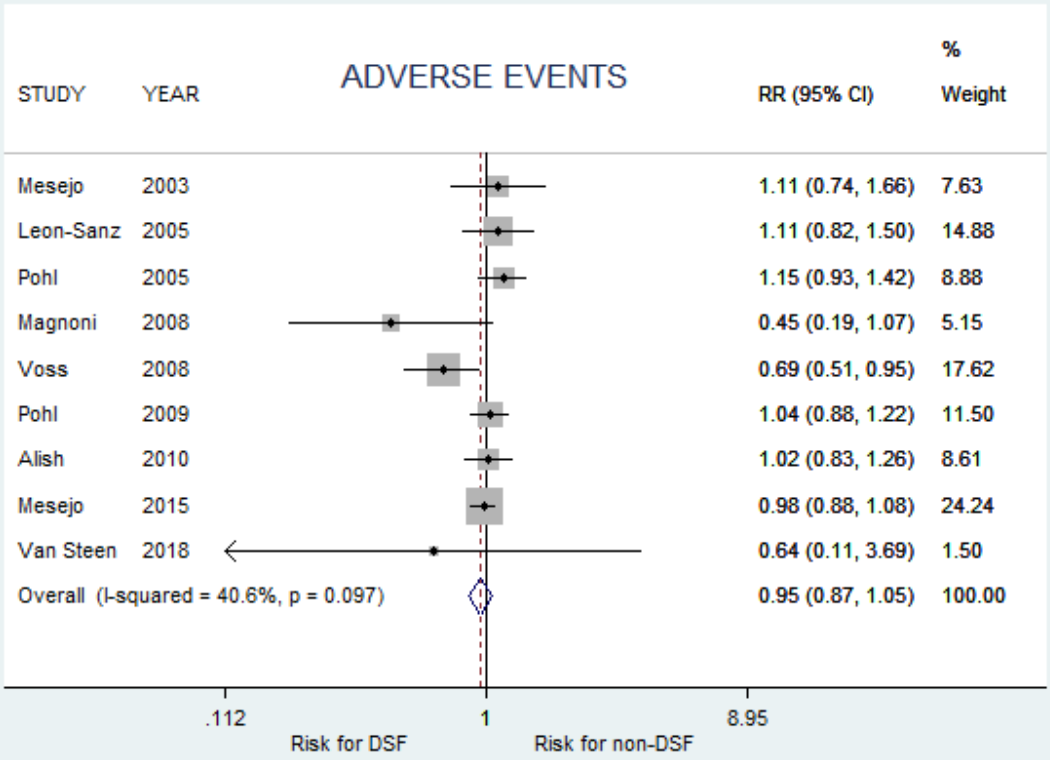

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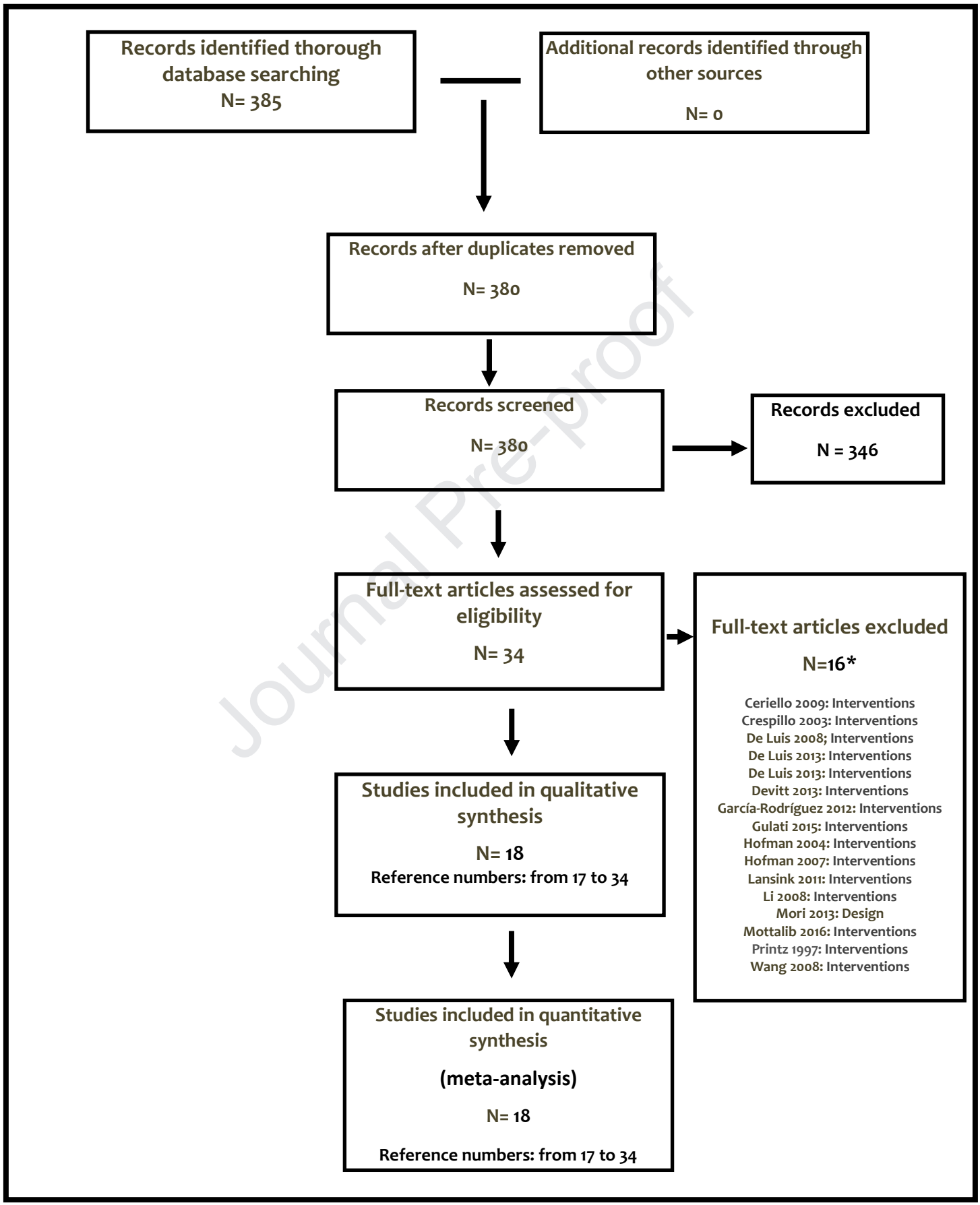
Figure 1. Flow diagram of systematic review methodology and process for studies inclusion.



*Sixteen full texts articles were excluded because design (not a randomized clinical trial) or interventions (enteral nutrition formula in the intervention group did not contain ≥ 20% of the total energy from MUFA or ≥ 40% of total energy from fats).