The impact of caloric restrictions on Type 2 diabetes

A meta-analysis

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15 August 2020

Contents

Introduction

Rationale

Diabetes is well spread chronic disease that limits patients lifestyles, leading to serious complications both macrovasculopathies, microvasculopathies, and might have effects on premature death. As a well known disease, many techniques have been elaborated in order to facilitate it's treatment by means of anti-diabetic medications, insulin injections, and even bariatric surgeries. As most of these methods are quite commonly used, they carry limitations. Healing Type 2 diabetes(T2B) has been difficult. In order to understand this further we will shortly distinguish Diabetes into 2 different parts: Type 1 and 2 diabetes.

Type 1 diabetes, is an abnormal chronic condition, in which an autoimmune destruction of beta cells in the pancreas does not produce in sufficiency or at all any insulin. This anabolic hormone is necessary in order to process the glucose. While Type 2 diabetes usually develops a resistance from cells to uptake insulin, although with normal insulin levels at first,it could evolve into an under-secretion of insulin. Type 2 diabetes is commonly correlated with weight gain,large BMI, and unhealthy diets. Therefore the anti-diabetic medications, insulin injections are taken for life, and are uncomfortable. Some perform bariatric surgeries in order to limit their weight and or fat levels. Although efficient, these procedures as they are interventional, are not without risks(operative and post-operative). Additionally, risks of relapse are high, if patients are not well accompanied by health workers in terms of diet and lifestyle change. Another limit to theses treatments are the cost and availability of the medications and access to surgery.

It is therefore in this context that the notion of caloric restrictions are thought of important subjects to investigate in their possible effect on improving the conditions of T2D patients. Caloric restrictions are defined in many ways, some tend towards diets (different types and different severity of diets were explored) and others are fasting (intermittent or continuous). This would enable a more cost effective approach. Improvement of t2d patients is also interpreted with multiple variables including HBA1c, FPG (fasting plasma glucose), weight mass, waist circumference, Basal hepatic glucose, HBO, time to discontinuation of insulin, hyper-tension, hyper-cholesterol... These various interpretations of measures defined by researchers, in the way the caloric restrictions are defined, and T2D outcomes, combined with many different covariates such as experimental designs, etc. are of interest in their combination to do a meta analysis, such as to better understand the relationship between caloric restrictions and T2D.

Objectives

The objective is to explore by the means of a meta-analysis what is the relationship between caloric restrictions and T2D. We will explore individual and combined effects of these studies to answer this question, and define how large these effects are, how do they differ from other studies. It is hoped to explore how large is the variation over studies. In other words this study analyses the magnitude of this relationship and specific direction of the relationship between both concepts.

Methods

Literature selection

The process of selection of the literature was conducted in a 3 step selection. In order to minimize bias, the selected sources were diversified into different search engines. As a first step a total of 4 search engines were chosen: 2 of which, Google Scholar and DuckDuck Go, were oriented towards a more general approach to information. The 2 other sources, PubMed and NCBI/PMC were more specific to the medical and biomedical field. On the last week of July 2020, combining the keywords “intermittent fasting”, “caloric restriction” and “diabetes type 2”, presented in Google Scholar 3200 results. DuckDuck Go does not provide a limited number of results /as you can see in link additional/, so the first 200 results were arbitrarily opted

as viable results. As for PubMed, the keywords “caloric restriction* diabetes type 2 fasting* intermittent” presented 14 results, while only using ""caloric restriction*" diabetes type 2" provided with 489 results. It was therefore decided to account for all the numbers of studies, summing up to 503 results. For the last source NCBI/PMC, using the combinations of the same keywords provided 17 studies. Accounting for all the various sources, a total of 3920 results are retained.

The second step consist of simultaneously, a selection and elimination process. On one side, gray literature was excluded. That was especially the case of DuckDuck Go that presented results out of the scope of scientific literature. On the other side, only the first top 100 results per source were considered. These elimination and selection processes are justified as scientific knowledge and more specifically the medical field bases its research predominantly on scientific literature. Moreover, this knowledge is build up on previous scientific discoveries, thus the method of selecting the first 100 can be justified, as it could account indirectly for older papers. In total, only 313 papers were saved for the third selection step.

The last selection step, was performed by excluding papers where the abstract, method, or outcome was not matching our questions. Additionally, animal testing and other alternative forms of experiment were excluded. Our selection process concluded with 7 papers for our meta analysis which can viewed in figure 2.

Information characteristics

It is crucial to understand that the construct of this meta analysis has many limits. Not only in the way the selection process has been built (which will be further discussed in the discussion section), but in the nature and characteristics of information. As seen in table 1, geography, language, and the age of the papers differ. In total 4 countries are represented in this meta analysis. Two out of seven papers (28.57%) represent results from the USA. The same percentages are applied to Canada and Australia. These three countries have the same weights in their representation in the meta analysis. However, the UK only represents 14.28% of the meta analysis. A consequence is that all the papers selected are only in English which limits our approach to this meta analysis. Concerning the reported dates of publication of each the studies the 6 out of 7 (or 85.71%) studies are between $2017 - 2020$. The studies of Lichtash et al. (2020) and Ku, Ramos, and Fung (2017) date of 2020, which make the year 2020 representing 28.57% of the meta analysis. The same logic applies to Furmli et al. (2018). and Lean et al. (2018) (2 studies) for the publishing date of 2018, which represents 42.85% (majority). Respectively Lean et al. (2018) and Henry, Scheaffer, and Olefsky (1985) weight 14.28%, but date of 2017 and 1985. It is noticeable that the dates are mainly focused on recent researches. It can be explained in two ways. Firstly, if the logic of medical sciences was considered, it is often build up on previous knowledge and old papers can quickly become out of date, if not overwritten with more recent research provided with better medical advances and technology. This would explain why older papers are less apparent in our meta analysis. Secondly, The selection process has a role to play as one of the steps was to only select the first 100 results per sources (if they were more). In consequence, the newer along with the most relevant papers tend to appear first. Therefore, careful attention needs to be paid to the interpretations, that still are not without bias.

Summary measures

The designs are not precisely the same in their interpretation of a caloric diet (as seen in table 1. While some focused on intermittent fasting such as Furmli et al. (2018), some others were oriented towards very low caloric diets, some of which were particular Keto diets and Low carbohydrates diets. Others opted for combinations of diets and/or fasting, which were applied at different stages of the experiment or simultaneously, as seen in Lichtash et al. (2020); Ku, Ramos, and Fung (2017) . Concurrently, evaluating diabetes can be done in a multitude of measures. As seen in table 3, the outcome measures are defined by the variation of average HBA1c (%), the variation of average weights (Kg), the variation of the average waist length, the variation of the average BMI and the mean absolute number of medication prescribed. There is no specific consensus with regards to the go to value of measuring T2D, as these values are often linked. Therefore, some studies take into account various variables, of which many are missing values and some

variables have missing standard deviations. Thus, two variables remain in our study: average variation of HBA1c and average variation of weight.

Having two different outcome variables implied a pertinence in applying a multilevel meta analysis. However, some challenges were faced by the lack of information provided for the correlation between the two outcomes: average variation of HBA1c and average variation of weight. This made it impossible to carry out the methods further. It was therefore decided to produce two unilevel meta analyses for each outcome, instead of choosing one.

Risk of Bias

The risk of bias is central in our analysis. It can be evaluated in two folds. Firstly, by assessing the risk of bias at the individual studies level, which will be analyzed via the traffic light plots (seen later on). Secondly, the risk of bias across studies will be evaluated by means of a publication bias. Funnel plots will be provided to visualize the bias. The Trim and Fill method (Duval and Tweedie 2000) would be of interest to be used in case a correction. However this won't be furthered in this study.

As seen in table 2, the citation structure provides better understanding of which papers are cited by other papers. Ku, Ramos, and Fung (2017) does not cite any of the other papers. Lichtash et al. (2020) appears at the same year as Ku, Ramos, and Fung (2017) Therefore they do no cite each other (same logic with both Carter, Clifton, and Keogh (2018)). However he cites Lean et al. (2018) and Furmli et al. (2018). Furmli et al. (2018) cites Lean et al. (2018) while Lean et al. (2018). is the only one that cites Henry, Scheaffer, and Olefsky (1985). As understood, the citations are not independent from each other.

Synthesis of results

The approach used in order to perform two unilevel analyses, bases itself of nesting structure of the accepted studies (Figure 2, Appendix). It is observed that the two different outcome measures were nested within samples, which were further nested within studies.
With this information, a fixed effects model would not be appropriate for the analysis. This can be justified as the effect sizes arise from a single population (Schwarzer, Carpenter, and Rücker 2015), whereas the characteristics of selected studies suggest that this would not be the case in our data. For this reason, the author decided to fit a random effects model with only one level (Study level), in the following form:

$$\begin{aligned} y_{ij} &= \beta_0 + u_i + \varepsilon_{ij} \\ u_i &\sim N(0, \tau^2) \\ \varepsilon_{ij} &\sim N(0, \sigma^2) \end{aligned}$$

Where y_{ij} is the percentage change of the HBA1c outcome in the ith study ($i = 1, \ldots, k$), $k = 5$ the total number of studies, β_0 represented the intercept, which is also the $E[Y_{ij}]$, u_i the random effect of the ith study, ε_{ij} the random residual, and finally τ^2 and σ^2 denoted the variance of their respective random components. This function is also applied for the weight change outcome.

Finally, for the estimation, the researcher decided to use Restricted Maximum Likelihood (REML) method (Sidik and Jonkman 2007; Viechtbauer 2005).

Additional analysis

Influential cases might be considered in order to assess the robustness of the effect estimate. Which would provide our analysis with some incites whether estimates depend heavily on specific studies. A common, method that could be performed is a Leave-One-Out-method (Harrer et al. 2019). This analysis won't be carried out in this papers, as only 5 papers are taken into account. It is advanced that the number of papers

is not large enough, thus it is argued that all the papers are crucial, such as leaving any paper would have a critical effect the estimates strongly.

As a mention, the analysis was carried out in `R` (R Core Team 2020). Of which details are displayed in the *Software Appendix*, complemented with the *Code Appendix*.

Results

Synthesis of results

Figure 3 and 4 demonstrate respectively both the results of the random effects models for HBA1c and Weight. Both will be presented here below.

In Figure 3, the effects show that the model estimates are negative across the studies. Varying from standard mean differences of -3.80 to -0.30, the random effect is consequently estimated to -1.40, with a strong significance ($p<0.01$). These results show that there is a significant decreasing effect of the variation of HBA1c (%) due to various caloric restrictions.
However, The result (red diamond) shows a bordering of the random effects standardized mean difference in a 95% CI. The upper limit reaches the 0.01, which could be disputable in terms of significance. Clarification can be made by adding additional studies into the analysis, or by analyzing the variation of the overall significance when a study is left-out. As mentioned before, it is still argued that with a limited number of studies most studies would be influential. Considering the weights of the studies, they seem to be balanced, except for Furmli et al. (2018) that has a lower weight of only 9.3% which could be a result of having a smaller sample size (N=3). As for the studies of Lichtash et al. (2020) and Ku, Ramos, and Fung (2017), the standard deviation could not be calculated due to only having one observation (N=1), therefore were excluded (weight =0) from the analysis. The I^2 (Higgins and Thompson (2002)) is a measure of the percentage of variability in the outcome that it is not caused by sampling error. It reported a $I^2 = 97\%$. This implies that strong heterogeneity between studies is present. In addition, it is then beneficial to study the between-study variance ($\tau^2 = 2.2448$). This provides a complimentary evidence that there is a considerable heterogeneity between studies.

The same analysis is done in Figure 4, the random effects show that the model estimates are strongly negative across the studies. Varying from standard mean differences of -16.50 to -0.50, the random effect is consequently estimated to -8.24, with a strong significance ($p<0.01$). These results show that there is a significant decreasing effect of the variation of weight (kilogram) due to various caloric restrictions. The weights of the studies seem to be overall balanced, except for Henry, Scheaffer, and Olefsky (1985) that has a slightly higher weight of only 21.5%. As for the studies of Lichtash et al. (2020) and Ku, Ramos, and Fung (2017). The I^2 (Higgins and Thompson (2002)) is a measure of the percentage of variability in the outcome that it is not caused by sampling error. It reported a $I^2 = 92\%$. This implies that strong heterogeneity is present. Again, it becomes beneficial to study the between-study variance reflects the variance of the true effect sizes, which showed a $\tau^2 = 4.6681$. This gives a complimentary approach to explain that the variance of the true effect size is quite high.

Overall both forest plots have shown strong significance of decreasing effects in respectively, the variation of HBA1c (%) and the variation of weight (kilograms) due to various caloric restrictions

Risk of bias

In analyzing the risk of bias, the traffic light plot is used to determine the bias at an individual study level. Figure 5, utilized the ROB (robvis) tool to demonstrated. Out of the 7 studies Lean et al. (2018) and the Carter, Clifton, and Keogh (2018) have the best results in terms of low overall bias across the 5 types. As for the studies of Furmli et al. (2018) and Henry, Scheaffer, and Olefsky (1985), they have an overall bias that poses some concerns. While the last two papers of Lichtash et al. (2020) and Ku, Ramos, and Fung (2017)

show high level of bias. This is especially the case as these are study cases. In which no specific selection process was described for example.

In addition to the bias individual study levels, the publication bias is crucial. Funnel plots have been done for each of the two outcomes in figure 6 and 7. As a first remark, in figure 6 the triangular region in which 95% of studies are expected to be contained in the absence of both biases and heterogeneity, is not respected (except for one study). Four of the points at the top of the funnel represent large sizes studies. As for the figure 7, three studies are situated within the funnel, however two are outside it. Which might indicate again bias and/or heterogeneity among other things such as poor methodological design etc. The funnels are both asymmetric, but the Trim and Fill method will not be applied. It is advanced that the major issue here, could be a lack of number of studies, which are enough to have an unclear idea of the real heterogeneity, bias of this analysis and a clear funnel-like shape.

Discussion

This meta-analysis analyzed 7 studies selected by a specific selection process which lead to some of the most relevant literature, with the aim to understand more clearly the relationship of performing a caloric restriction on improving type 2 diabetes. This is an interesting study as it could possibly replace life-long medication and even treat the patients. Using a random effects model, the results indicated a strong evidence in rejecting a null effect. Which would imply confirming breaking through research.

Limitations

As much as this meta analysis sounds promising, many limits are found. A better understanding of this study would be able by applying this to a larger scale of studies. Seven studies were clearly not substantial enough to fully understand the scope of the link between the two notions. As much as two outcomes have been used to perform two sets of unilevel analysis, expanding the link to other outcomes that actually exist but were not evaluated by all studies uniformly, would have been advantageous in a better understanding of the link. Furthermore, a multilevel analysis would have been interesting, had papers provided correlation between outcomes.

The lack of clarity in defining the exact notions needed, is indeed a limitation not only in the multitude of outcomes, but as well in circling the notion of caloric restriction, that could be extremely various. The studies opted for different application of restriction. For example, even when the notions where the same, such as using intermittent fasting, the application itself could be different, as some fasted on liquids others didn't replicate the same experiment. They also fasted for different number of hours depending on patients. The design of the experiments was not standard per say. The selection itself and procedures of the individual papers were not all randomized, or even elaborated in the same manner.

Additionally, the selection process of this analysis itself was not without bias. Indirectly this promoted only the most recent and relevant papers (also cited), excluding other possibly relevant information that could have emerged from gray literature. Not only are the studies limited by their linguistic and geographical approach, resulting in a bias in term of variety. But a few of the papers had very small sample size, which is recurrent in the medical field, and even lead to study cases (N=1), two of which were present in this analysis hindered the power of the paper for such a small amount of papers analyzed.

Although some assessment of risk of bias was presented, in the way of using the ROB2 tool and a publication bias via funnel plots, both of these methods are very limited. Firstly as the ROB2 tool is used with the assumption of randomized trials, not all the studies are exactly so. Secondly, the funnel plots are not confirmatory in the determination of heterogeneity or bias, but more so as possible indicators. Both tools used could have had some other alternatives that would better the understanding of bias and heterogeneity. Such as replacing ROB2 with ROB1 and complementing the funnel plots with significance tests.

Conclusions

This meta-analysis shows evidence for a significant effect of caloric restrictions on T2D by the outcomes of the average variation of HBA1c in percentage and average variation of weight in kg. However, considerable attention should be paid with many limits in terms of bias and especially in the numbers of papers accounted for.

Appendix

Table 1: Studies characteristics

ID	Author	Country	Type of Caloric Restriction
1	Henry et al. (1985)	USA	Very low caloric diet
2	Lean et al. (2017)	UK	Weight management programme, 3 phase
3	Furmli et al. (2018)	CANADA	Intermitent Fasting
4	Carter et al. (2018) (a)	AUSTRALIA	Intermitent Fasting
5	Carter et al. (2018) (b)	AUSTRALIA	Continuous energy restriction
6	Lichtash et al. (2020)	USA	Intermitent Fasting and Keto diet
7	Ku et al. (2020)	CANADA	Intermittent Fasting and Low carbohydrate diet

(a, b): Same study, different caloric restriction

Table 2: Citation structure

		ID						
ID	Author	1	2	3	4	5	6	7
1	Henry et al. (1985)	-	-	-	-	-	-	-
2	Lean et al. (2017)	X	-	-	-	-	-	-
3	Furmli et al. (2018)	O	X	-	-	-	-	-
4	Carter et al. (2018) (a)	O	W	W	-	-	-	-
5	Carter et al. (2018) (b)	O	W	W	O	-	-	-
6	Lichtash et al. (2020)	O	X	X	O	O	-	-
7	Ku et al. (2020)	O	O	O	O	O	W	-

X: cited.

O: not cited.

W: within a year, not cited.

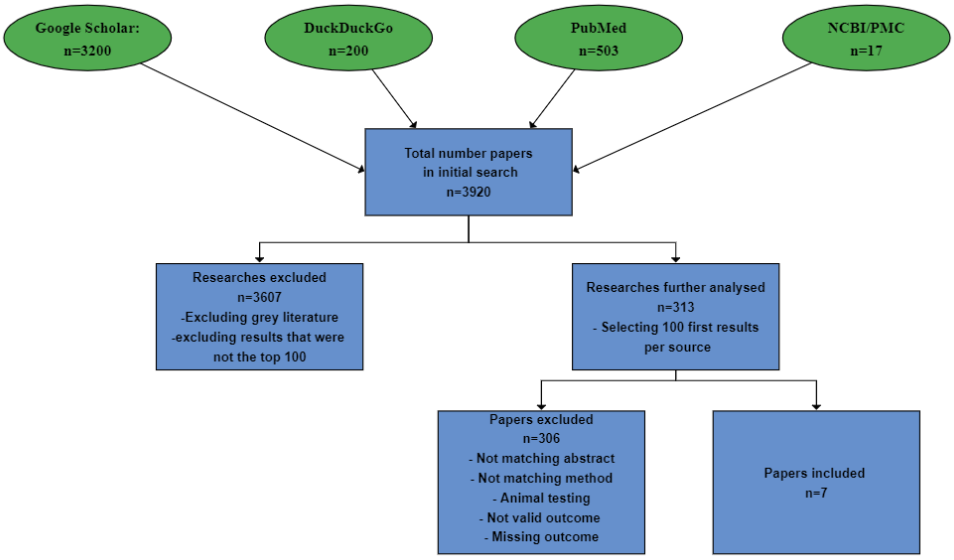

Figure 1: Flowchart: Paper selection process

Figure 2: Flowchart: Paper selection process

Table 3: Outcome measures of the studies

ID	Author	N	Male (%)	Mean age	Mean history of diabetes (years)	Outcome measures				
						HBA1c (Var. %)	Weight (Var. Kg.)	Waist lenght (Var. cm.)	BMI (Var. units)	Mean number of prescribed medication (Var. units)
1	Henry et al. (1985)	30	0.10	53.00	9.00	−3.80	−10.50	NA	NA	NA
2	Lean et al. (2017)	306	0.56	52.90	3.00	−0.85	−8.80	NA	NA	0.00
3	Furmli et al. (2018)	3	1.00	53.00	18.33	−1.93	−9.87	−15.00	NA	−5.00
4	Carter et al. (2018) (a)	70	0.44	61.00	7.90	−0.30	−5.00	NA	−2.30	NA
5	Carter et al. (2018) (b)	67	0.43	61.00	8.10	−0.50	−6.80	NA	−1.90	NA
6	Lichtash et al. (2020)	1	0.00	57.00	15.00	−3.50	−4.30	NA	−1.60	−1.00
7	Ku et al. (2020)	1	1.00	69.00	35.00	−0.50	−16.50	−12.00	NA	−5.00

NA: Not Available

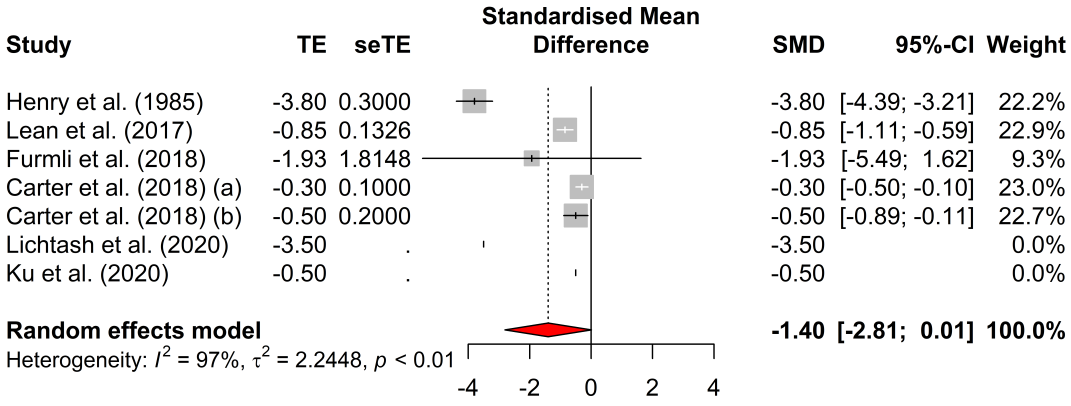

Figure 3: Forrest plot, HAB1c percentage variation

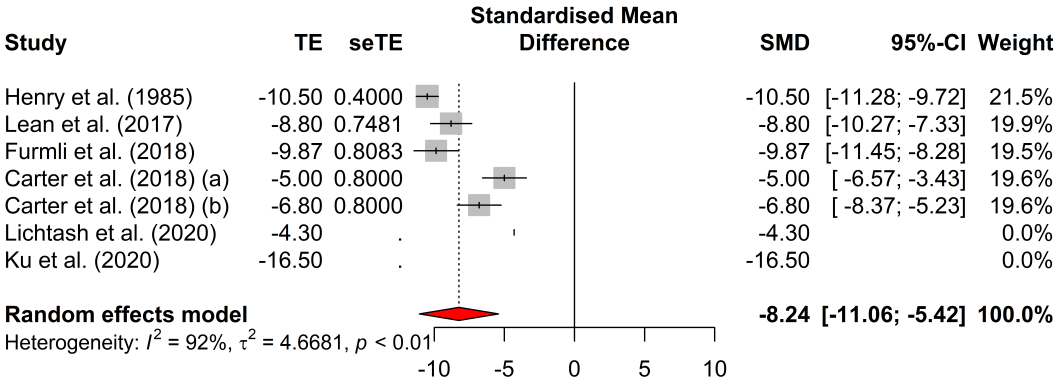

Figure 4: Forrest plot, Weight difference in kilograms

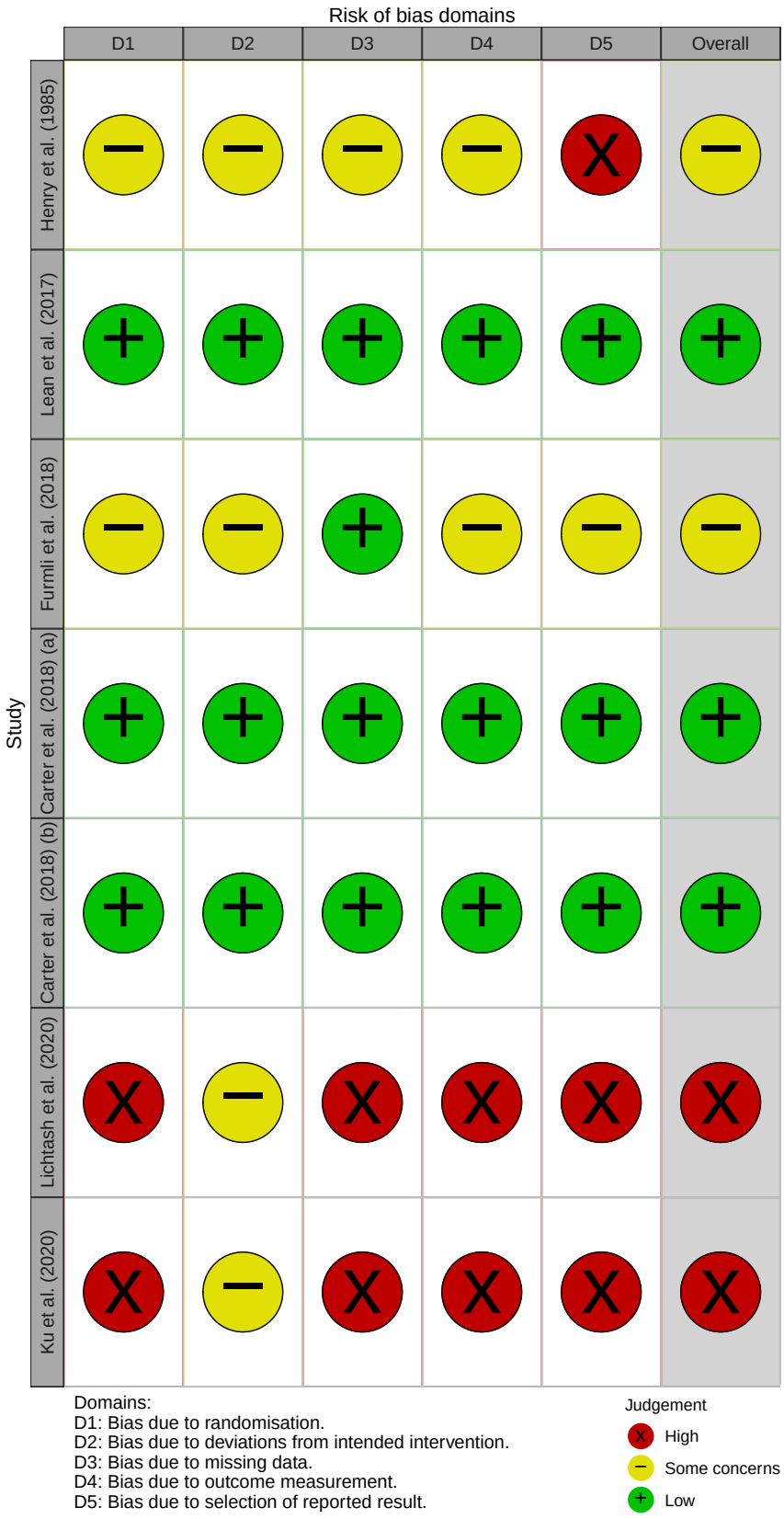

Figure 5: Traffic plot, ROB tool

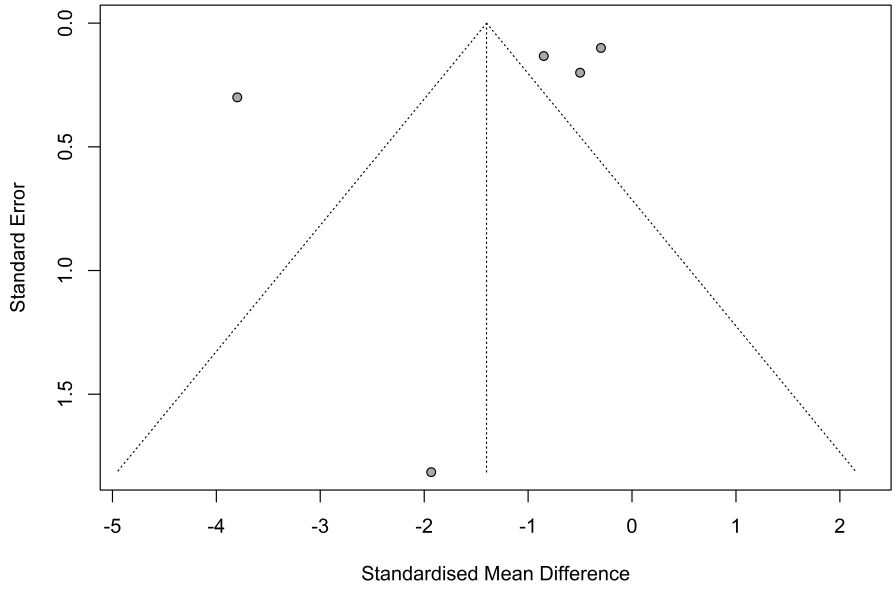

Figure 6: Funnel plot, publication bias on HAB1c outcome

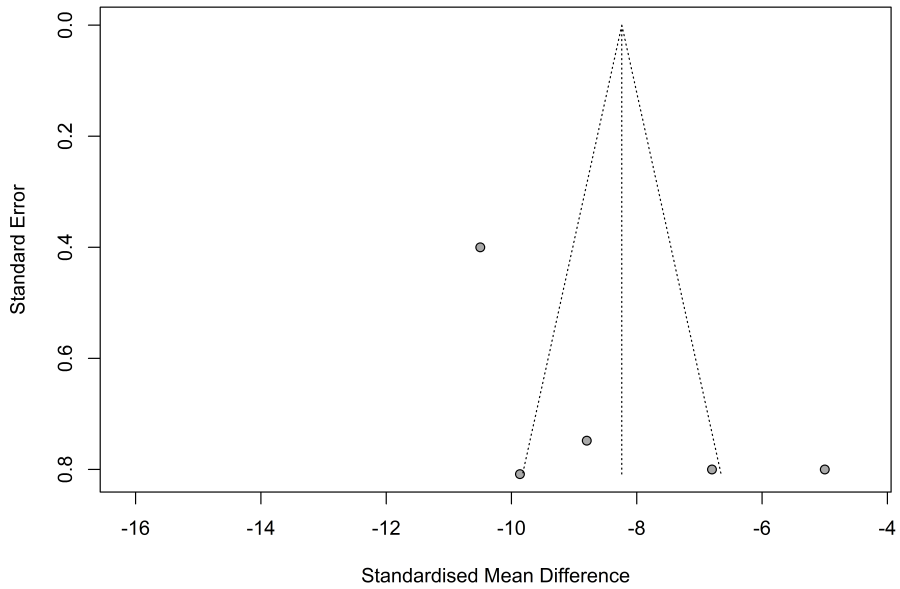

Figure 7: Funnel plot, publication bias on weight outcome

Software Appendix

```
## R version 4.0.2 (2020-06-22)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 18363)
##
## Matrix products: default
##
## locale:
## [1] LC_COLLATE=English_Belgium.1252  LC_CTYPE=English_Belgium.1252
## [3] LC_MONETARY=English_Belgium.1252 LC_NUMERIC=C
## [5] LC_TIME=English_Belgium.1252
##
## attached base packages:
## [1] grid      stats     graphics  grDevices utils     datasets  methods
## [8] base
##
## other attached packages:
##  [1] meta_4.13-0     metafor_2.4-0   Matrix_1.2-18   ggpubr_0.4.0
##  [5] ggrepel_0.8.2   gridExtra_2.3   ggthemes_4.2.0  webshot_0.5.2
##  [9] glue_1.4.1      gt_0.2.2        reshape2_1.4.4  forcats_0.5.0
## [13] stringr_1.4.0   dplyr_1.0.1     purrr_0.3.4     readr_1.3.1
## [17] tidyr_1.1.1     ggplot2_3.3.2   tidyverse_1.3.0 readxl_1.3.1
## [21] tibble_3.0.3    haven_2.3.1     knitr_1.29      tinytex_0.25
##
## loaded via a namespace (and not attached):
##  [1] nlme_3.1-148       fs_1.5.0           lubridate_1.7.9    RColorBrewer_1.1-2
##  [5] httr_1.4.2         tools_4.0.2        backports_1.1.8    R6_2.4.1
##  [9] DBI_1.1.0          colorspace_1.4-1   withr_2.2.0        processx_3.4.3
## [13] tidyselect_1.1.0   curl_4.3           compiler_4.0.2     cli_2.0.2
## [17] rvest_0.3.6        xml2_1.3.2         sass_0.2.0         checkmate_2.0.0
## [21] scales_1.1.1       callr_3.4.3        digest_0.6.25      foreign_0.8-80
## [25] minqa_1.2.4        rmarkdown_2.3      rio_0.5.16         pkgconfig_2.0.3
## [29] htmltools_0.5.0    lme4_1.1-23        dbplyr_1.4.4       rlang_0.4.7
## [33] rstudioapi_0.11    farver_2.0.3       generics_0.0.2     jsonlite_1.7.0
## [37] zip_2.0.4          car_3.0-8          magrittr_1.5       Rcpp_1.0.5
## [41] munsell_0.5.0      fansi_0.4.1        abind_1.4-5        lifecycle_0.2.0
## [45] stringi_1.4.6      yaml_2.2.1         CompQuadForm_1.4.3 carData_3.0-4
## [49] MASS_7.3-51.6      plyr_1.8.6         blob_1.2.1         crayon_1.3.4
## [53] lattice_0.20-41    splines_4.0.2      hms_0.5.3          ps_1.3.3
## [57] pillar_1.4.6       boot_1.3-25        ggsignif_0.6.0     codetools_0.2-16
## [61] reprex_0.3.0       evaluate_0.14      data.table_1.13.0  modelr_0.1.8
## [65] vctrs_0.3.2        nloptr_1.2.2.2     cellranger_1.1.0   gtable_0.3.0
## [69] assertthat_0.2.1   xfun_0.16          openxlsx_4.1.5     broom_0.7.0
## [73] rstatix_0.6.0      statmod_1.4.34     ellipsis_0.3.1
```

Code Appendix

```
# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
# Section       : Preliminar
# SubSection    : None
# SubSubSection : None
# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
rm(list=ls())

# libraries
libraries <- c('tinytex','knitr','haven','tibble','readxl','tidyverse','stringr',
               'dplyr','reshape2','gt','glue','webshot','ggplot2','ggthemes',
               'grid','gridExtra','ggrepel','ggpubr','forcats','metafor','meta',
               'robvis')
sapply(libraries, require, character.only=T)
# install.packages(libraries)


options(tinytex.verbose = TRUE)

opts_chunk$set(fig.align='center',
               size='small',
               external=TRUE,
               cache=TRUE,
               message=FALSE,
               warning=FALSE,
               error=FALSE,
               echo=FALSE,
               include=FALSE,
               fig.pos='H')


# load
# dir_data <- file.path(file.choose())
file_dir <- 'D:/documents/Master Statistics/Q2/metaanalysis/project'
dir_data <- file.path(file_dir,'metaanalysis.xlsx')
studies <- read_excel(dir_data, sheet='S')
citation <- read_excel(dir_data, sheet='C')
rob <- read_excel(dir_data, sheet='R')
# robis <- read_excel(dir_data, sheet='R')


# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
# Section       : Methods
# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
# creation: table of full papers table
image_dir <- 'D:/documents/Master Statistics/Q2/metaanalysis/project/images'

var_int <- c('NBR','IDENTIFICATION','Country','Caloric_restriction_type')

gt(data=studies[, var_int]) %>%
  cols_label(
    NBR='ID',
```

```
    IDENTIFICATION='Author',
    Country='Country',
    Caloric_restriction_type='Type of Caloric Restriction') %>%
  tab_header(
    title='Table 1: Studies characteristics') %>%
  tab_source_note(
    source_note='(a, b): Same study, different caloric restriction') %>%
  gtsave('literature_char1.png', path=image_dir)


# plotting: table of full papers table
knitr::include_graphics(file.path(image_dir, 'literature_char1.png'))


# creation: table of citation structure
data_mom <- citation
# str(data_mom)

data_mom[,3:9] <- lapply(data_mom[,3:9],
                         factor,
                         level=c('X','O','W','-'))

# str(data_mom)

gt(data=data_mom) %>%
  cols_label(
    NBR='ID',
    IDENTIFICATION='Author') %>%
  tab_header(
    title='Table 2: Citation structure') %>%
  tab_spanner(
    label='ID',
    columns=3:9) %>%
  data_color(
    columns=3:9,
    colors=c('grey','blue','green','white'),
    alpha=0.5,
    apply_to='fill',
    autocolor_text=T) %>%
  tab_source_note(
    source_note='X: cited.') %>%
  tab_source_note(
    source_note='O: not cited.') %>%
  tab_source_note(
    source_note='W: within a year, not cited.') %>%
  gtsave('literature_char2.png', path=image_dir)


# plotting: table of citation structure
knitr::include_graphics(file.path(image_dir, 'literature_char2.png'))


# plotting: flowchart of filtered papers
```

```r
knitr::include_graphics(file.path(image_dir,'figure2.png'))


# plotting: table of full papers table
knitr::include_graphics(file.path(image_dir, 'Classification diagram.png'))


# creation: table of rejected studies
col_int <- c('NBR','IDENTIFICATION','TNP','PERC_MALE','AVG_AGE',
             'duration_diabetes','HBA1c_CHG_PER','WEIGHT_CHG',
             'WAIST_CHG','BMI_CHG','CHG__MEANDRUGPRESC')
data_mom <- studies[, col_int]
data_mom[,9:11] <- sapply(data_mom[,9:11],
                          as.numeric)


gt(data=data_mom) %>%
  cols_label(
    NBR='ID',
    IDENTIFICATION='Author',
    TNP='N',
    PERC_MALE='Male (%)',
    AVG_AGE='Mean age',
    duration_diabetes='Mean history of diabetes (years)',
    HBA1c_CHG_PER='HBA1c (Var. %)',
    WEIGHT_CHG='Weight (Var. Kg.)',
    WAIST_CHG='Waist lenght (Var. cm.)',
    BMI_CHG='BMI (Var. units)',
    CHG__MEANDRUGPRESC='Mean number of prescribed medication (Var. units)') %>%
  fmt_number(
    columns=vars(PERC_MALE,AVG_AGE,duration_diabetes,HBA1c_CHG_PER,
                 WEIGHT_CHG,WAIST_CHG,BMI_CHG,CHG__MEANDRUGPRESC),
    decimals=2) %>%
  tab_header(
    title='Table 3: Outcome measures of the studies') %>%
  tab_spanner(
    label='Outcome measures',
    columns=7:11) %>%
  tab_source_note(
    source_note='NA: Not Available') %>%
  cols_width(
    vars(NBR) ~ px(50),
    vars(IDENTIFICATION) ~ px(165),
    vars(TNP) ~ px(50),
    vars(PERC_MALE) ~ px(70),
    vars(AVG_AGE) ~ px(70),
    vars(duration_diabetes) ~ px(70),
    vars(HBA1c_CHG_PER) ~ px(70),
    vars(WEIGHT_CHG) ~ px(70),
    vars(WAIST_CHG) ~ px(80),
    vars(BMI_CHG) ~ px(70),
    vars(CHG__MEANDRUGPRESC) ~ px(110)) %>%
  gtsave('literature_char3.png', path=image_dir)
```

```r
# plotting: table of rejected studies
knitr::include_graphics(file.path(image_dir, 'literature_char3.png'))


# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
# Section       : Results
# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
# data meta1
col_int <- c('NBR','IDENTIFICATION','TNP','HBA1c_CHG_PER','VAR_HBA1C')
data_meta1 <- studies[, col_int]
data_meta1$VAR_HBA1C <- as.numeric(data_meta1$VAR_HBA1C)

# meta-analysis model
meta1 <- metagen(HBA1c_CHG_PER,
                 seTE=VAR_HBA1C,
                 data=data_meta1,
                 studlab=IDENTIFICATION,
                 comb.fixed = FALSE,
                 comb.random = TRUE,
                 prediction=FALSE,
                 sm="SMD",
                 method.tau='REML')
# meta1


# creation: forest plot (no covariates)
file_save <- file.path(image_dir,'meta1.png')
png(filename=file_save, width=20, height=8, units='cm', res=1000)
forest(meta1, col.diamond="red")
dev.off()


# plotting: forest plot
knitr::include_graphics(file.path(image_dir,'meta1.png'))


# data meta2
col_int <- c('NBR','IDENTIFICATION','TNP','WEIGHT_CHG','VAR_WEIGHT')
data_meta2 <- studies[, col_int]
data_meta2$VAR_WEIGHT <- as.numeric(data_meta2$VAR_WEIGHT)

# meta-analysis model
meta2 <- metagen(WEIGHT_CHG,
                 seTE=VAR_WEIGHT,
                 data=data_meta2,
                 studlab=IDENTIFICATION,
                 comb.fixed = FALSE,
                 comb.random = TRUE,
                 prediction=FALSE,
                 sm="SMD",
                 method.tau='REML')
# meta2
```

```r
# creation: forest plot (country effects)
file_save <- file.path(file_dir, 'meta2.png')
png(filename=file_save, width=20, height=8, units='cm', res=1000)
forest(meta2, col.diamond="red")
dev.off()


# plotting: forest plot
knitr::include_graphics(file.path(image_dir,'meta2.png'))


# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
# Section       : Risk of bias
# %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
rob_traffic_light(data=rob[,2:ncol(rob)], tool="ROB2")


# creation: funnel plot
file_save <- file.path(file_dir, 'meta1_funnel1.png')
png(filename=file_save, width=20, height=15, units='cm', res=1000)
funnel(meta1, pch=19) +
dev.off()

# plotting: funnel plot
knitr::include_graphics(file.path(image_dir, 'meta1_funnel.png'))


# creation: funnel plot
file_save <- file.path(file_dir, 'meta2_funnel.png')
png(filename=file_save, width=20, height=15, units='cm', res=1000)
funnel(meta2, pch=19)
dev.off()


# plotting: funnel plot
knitr::include_graphics(file.path(image_dir, 'meta2_funnel.png'))


# ============================================================================
# Section:        Software Appendix
# SubSection:     None
# ============================================================================
sessionInfo()
```

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