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Bachelor Thesis

Personalized treatment effects in diabetology – A meta-analysis based on the coefficient of variation

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Contents

Abstract

As the prevalence of diabetes increases worldwide, it is important to continue research in this field. The majority of people who have diabetes suffer from type 2 diabetes. One consequence of the increasing number of patients is the increasing burden on the health care system. Furthermore, diabetes can cause some secondary complications, such as cardiovascular diseases.

One possible approach improving the treatment of diabetes is precision medicine. The optimization of treatment, but also of diagnosis, prediction and prevention, is performed by using knowledge about human biological variation and multidimensional data (e.g. electronic medical records), with attention to the individual characteristics of each patient.

At the moment, the potential of precision medicine in the treatment of type 2 diabetes is still unknown. The aim of this thesis is to quantify this potential. This is done using the CVR, the coefficient of variation ratio, of the HbA_{1c} level after treatment. A coefficient of 1 is equivalent to equal variability in the treatment and control group. A coefficient greater than 1 is equivalent to a higher variability in the treatment group compared to the control group. This would indicate that there is a heterogeneous treatment effect and, therefore, potential for precision medicine.

A meta-analysis was performed because the estimate of the overall effect is more precise when several studies are combined. The data basis for this is provided by the systematic reviews by Palmer et al. and Tsapas et al. To consider the between-study variation, a random effects model was applied. The analysis was conducted in R with the *metafor* package. Finally, 174 studies were included in the meta-analysis. The remaining trials did not provide sufficient information on the number of study particicpants who completed the study and the HbA_{1c} level after treatment incl. standard deviation to be included in the analysis. The overall estimate for the CVR is 1.034 (95% CI 1.007 to 1.062) with a p-value of 0.0147. Consequently, the result is statistically significant at a 5% level. However, the effect is so close to 1 that the result is not clinically relevant. It can be assumed that there is almost no potential for precision medicine in type 2 diabetes.

List of Abbreviations

BMI	body mass index
CI	confidence interval
CVR	coefficient of variation ratio
HbA_{1c}	glycated hemoglobin A_{1c}
IQR	interquartile range
ITT	Intention-To-Treat
RCT	randomized controlled trial
RR	response ratio
VR	variability ratio

1 Introduction

The best-known forms of diabetes are type 1 diabetes and type 2 diabetes. Additionally, there is the rare monogenic diabetes which is the result of single gene mutations. Maturity Onset Diabetes of the Young (MODY) is part of this form (Antosik et al., 2016, p. S157). For this subtype, the precision medicine approach has already proven to be very successful. The treatment response differs depending on which gene the mutation is in. The resulting subgroups without any overlapping are the reason why the precision medicine approach is well suited for monogenic diabetes. Thus, some patients need no treatment at all and others respond well to the treatment with low doses of sulfonylureas. In type 2 diabetes, this approach is more difficult to implement because it is a polygenic disease which is also influenced by the environment. Therefore, the definition of individual subgroups is more complicated. Alternatively, subgroups can be defined based on the differences in treatment response to several drugs. Patient characteristics such as sex, BMI or certain biomarkers should be used for identification of the subgroups. The aim is to use this information to calculate how effective the treatment will be. A success of this approach would be desirable, as it would be easy to realise (Hattersley et al., 2017, pp. 769-776).

The aim of the following thesis is to find out whether there is potential for precision medicine in type 2 diabetes. For this purpose, a meta-analysis of variance is conducted. The data basis is constituted by several RCTs from which the relevant data are extracted.

The work is structured as follows: First, it is explained what precision medicine is and why the field of diabetology in particular is such an interesting one. In the next chapter, the statistical methods used are described. Afterwards, it is clarified on which data the conducted meta-analysis is based, how the data was processed and how the analysis was carried out. Finally, the limitations of the conducted meta-analysis are discussed, which alternatives exist and what the result of the analysis implies.

2 Epidemiology of type 2 diabetes and precision medicine approach

The field of diabetology is a very interesting and important area of research due to the increasing prevalence worldwide (Tönnies et al., 2019, p. 1217). The resulting problem can be well explained using Germany as an example. According to current calculations, ~ 6.7 million people in Germany suffer from diabetes. Most of the affected people have type 2 diabetes (Jacobs, Hoyer, Brinks, Icks et al., 2017, p. 855). The aim of the study by Tönnies et al. was the projection of the case numbers of type 2 diabetes in Germany between 2015 and 2040. Data from every person insured by the statutory health insurance and estimates for the type 2 diabetes incidence and mortality were used in a illness-death model for the calculation. Different scenarios regarding temporal trends in incidence and mortality rates were considered, yielding different results. According to the projections, between 10.7 million (+54%) and 12.3 million (+77%) type 2 diabetes cases are expected in Germany in 2040 (Tönnies et al., 2019, pp. 1217-1219). As the burden of diabetes patients on the health care system is already high, this problem will increase over the years. In 2010, the average annual cost per capita for people with type 2 diabetes was €5 146 in Germany. For people without type 2 diabetes, the average annual cost per capita was only €1956. Accordingly, health care expenditure for people with type 2 diabetes was 2.6-fold higher than for people without diabetes (Jacobs, Hoyer, Brinks, Icks et al., 2017, pp. 855-857). Furthermore, diabetes belongs to the ten most common causes of death worldwide because many people with diabetes die of cardiovascular diseases. Indeed, 16% of all deaths in Germany are associated with type 2 diabetes in 2010 (Jacobs, Hoyer, Brinks, Kuss et al., 2017, pp. 1703-1706).

Therefore, it is very important to treat type 2 diabetes in the right way. The aim of every clinician has always been to provide the best treatment for every patient. Today, increasing knowledge about human biological variation is opening up a wide range of new possibilities. Combined with information from electronic medical records, knowledge about lifestyle and environment and big data analytical methods, new devices are emerging for the identification of various predictors of treatment response. For diabetes in particular, the idea of precision medicine is very meaningful, as it offers hope that

the growing burden of diabetes will be reduced (Chung et al., 2020, p. 1672). Precision diabetes medicine can be generally defined as 'an approach to optimise the diagnosis, prediction, prevention or treatment of diabetes by integrating multidimensional data, accounting for individual differences' (Chung et al., 2020, p. 1675). This data can originate from traditional medical records, but also from big data (e.g. sensors for blood glucose measuring). At the same time, patient preferences, individual outcomes and cost-effectiveness are also taken into account. All this is highly relevant in type 2 diabetes, which is a very heterogeneous disease with many different representations. There are different treatment options, e.g. patient education and a resulting lifestyle adjustment, but also drugs for lowering the HbA_{1c} level. For each treatment option, the treatment response is highly variable among several patients. The aim of precision treatment is to find an appropriate treatment for each patient based on their individual characteristics, with the least possible side effects (Chung et al., 2020, pp. 1675-1683). At the current time, the potential for precision medicine in diabetes type 2 is still unknown.

3 Methods

3.1 Meta-analysis

In medicine, there are typically several studies carried out for one research question. However, the results of these studies can be partly contradictory. A meta-analysis tries to solve this problem by combining the results of multiple independent studies. These studies are usually RCTs (Haidich, 2010, pp. 29-30).

Meta-analysis can be defined as 'a quantitative, formal, epidemiological study design used to systematically assess the results of previous research to derive conclusions about that body of research' (Haidich, 2010, pp. 29-30). Systematic reviews that aim to gather available knowledge on a particular research question often include meta-analyses (Haidich, 2010, p. 30).

The treatment effect estimates from meta-analyses are often more accurate than the estimates from individual studies. But for this purpose, it is necessary to include as many trials as possible to avoid publication bias. This bias occurs because published studies can differ systematically from non-published studies. For example, studies with a significant, positive result are published with a higher probability than studies with a non-significant, negative result. Hence, it is often necessary to look for information outside the published literature. Whether publication bias is present can be checked by a funnel plot after the meta-analysis has been carried out. A symmetric inverted funnel shape suggests no existing publication bias (Haidich, 2010, pp. 30-34).

Meta-analysis distinguishes between two different models: a fixed effect model and a random effects model (Haidich, 2010, p. 32).

The fixed effect model is based on the assumption that all estimated effects are from one homogeneous population (Schwarzer et al., 2015, p. 28). To be concrete, this means that study population, subject selection criteria and way of treatment are the same in each study (Haidich, 2010, p. 32). $\widehat{\theta}_k$ is the estimated treatment effect from study k assuming that $k = 1, \ldots, K$ studies are included in the analysis. The aim is to estimate the treatment effect θ in the population. So, the associated fixed effect model is given by

$$\widehat{\theta}_k = \theta + \sigma_k \epsilon_k$$

with $\epsilon_k \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0, 1)$. In this case, $\widehat{\sigma}_k^2$ is the sample estimate of $\text{Var}\left(\widehat{\theta}_k\right)$. $\widehat{\theta}_F$ is the fixed

effect estimate of θ which can be determined using the maximum-likelihood principle with given estimates $\left(\widehat{\theta}_k, \widehat{\sigma}_k\right)$ by

$$\widehat{\theta}_F = \frac{\sum_{k=1}^{K} \widehat{\theta}_k / \widehat{\sigma}_k^2}{\sum_{k=1}^{K} 1/\widehat{\sigma}_k^2} = \frac{\sum_{k=1}^{K} w_k \widehat{\theta}_k}{\sum_{k=1}^{K} w_k}.$$

This is also referred to as the *inverse variance method* with weights $w_k = \frac{1}{\widehat{\sigma}_k^2}$ (Schwarzer et al., 2015, p. 28). These weights are supposed to represent the evidence of the studies. Thus, small studies are given less weight than large studies and low-quality studies (e.g. no control of measurement variation) are given less weight than high-quality studies (Haidich, 2010, p. 32). The estimation of the variance of $\widehat{\theta}_F$ can be expressed as

$$\widehat{\mathrm{Var}}\left(\widehat{\theta}_F\right) = \frac{1}{\sum_{k=1}^{K} w_k}.$$

Therefore, the $(1-\alpha)$ CI for $\hat{\theta}_F$ can be calculated using

$$\widehat{\theta}_F \pm z_{1-\frac{\alpha}{2}} \, \mathrm{SE}\left(\widehat{\theta}_F\right)$$

with the standard error $\mathrm{SE}\left(\widehat{\theta}_F\right) = \sqrt{\widehat{\mathrm{Var}}\left(\widehat{\theta}_F\right)}$ and the $1-\frac{\alpha}{2}$ quantile of the standard normal distribution $z_{1-\frac{\alpha}{2}}$ (Schwarzer et al., 2015, pp. 28-29).

In comparison, the random effects model is based on the assumption that the estimated effects vary and do not come from one homogeneous population (Schwarzer et al., 2015, p. 34). Specifically, this means that the effects are heterogeneous between studies with heterogeneity parameter τ^2. However, if the heterogeneity (variability in the treatment effects, between-study variance) is very high, it does not make sense to present an overall estimator, despite the random effects model (Haidich, 2010, pp. 32-33). The random effects model is given by

$$\widehat{\theta}_k = \theta + \mu_k + \sigma_k \epsilon_k$$

with $\epsilon_k \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0,1)$ and $\mu_k \overset{\text{i.i.d.}}{\sim} \mathcal{N}\left(0, \tau^2\right)$ whereby ϵ_k and μ_k are assumed to be independent. Since μ_k is drawn independently from $\mathcal{N}\left(0, \tau^2\right)$, μ_k is a random value. As a result, conducting study k again does not necessarily lead to the same μ_k. This is also called *exchangeability assumption*. For $\tau^2 = 0$, a fixed effect model is obtained. There are many ways of estimation, e.g. the DerSimonian-Laird estimator. The weighted sum of squares about the fixed effect estimate can be expressed as

$$Q = \sum_{k=1}^{K} w_k \left(\widehat{\theta}_k - \widehat{\theta}_F\right)^2$$

with $w_k = \frac{1}{\widehat{\sigma}_k^2}$. If $Q < (K-1)$, then $\widehat{\tau}^2 = 0$ and $\widehat{\theta}_R = \widehat{\theta}_F$. Otherwise, the definition

$$S = \sum_{k=1}^{K} w_k - \frac{\sum\limits_{k=1}^{K} w_k^2}{\sum\limits_{k=1}^{K} w_k}$$

is needed for estimating the heterogeneity parameter

$$\widehat{\tau}^2 = \frac{Q - (K-1)}{S}.$$

The random effects estimate $\widehat{\theta}_R$ of θ and its variance can be estimated by

$$\widehat{\theta}_R = \frac{\sum\limits_{k=1}^{K} w_k^* \widehat{\theta}_k}{\sum\limits_{k=1}^{K} w_k^*}$$

$$\widehat{\mathrm{Var}}\left(\widehat{\theta}_R\right) = \frac{1}{\sum\limits_{k=1}^{K} w_k^*}$$

with weights $w_k^* = \frac{1}{\widehat{\sigma}_k^2 + \widehat{\tau}_k^2}$. Due to the weights, this is also referred to as *inverse variance method*. Hence, the $(1-\alpha)$ CI for $\widehat{\theta}_R$ can be calculated using

$$\widehat{\theta}_R \pm z_{1-\frac{\alpha}{2}} \, \mathrm{SE}\left(\widehat{\theta}_R\right)$$

with the standard error $\mathrm{SE}\left(\widehat{\theta}_R\right) = \sqrt{\widehat{\mathrm{Var}}\left(\widehat{\theta}_R\right)}$ and the $1 - \frac{\alpha}{2}$ quantile of the standard normal distribution $z_{1-\frac{\alpha}{2}}$ (Schwarzer et al., 2015, pp. 34-35).

The most common method of presenting the results of a meta-analysis are forest plots. They show all studies with their effect sizes incl. 95% CI and, additionally, the pooled effect of the model incl. 95% CI (Haidich, 2010, p. 33).

Q is also the test statistic of Cochran's Q. This statistical test can be used to check for the presence of heterogeneity. The null hypothesis is the equality of means, accordingly $H_0 = \theta_1 = \theta_2 = \ldots = \theta_K$. Under the null hypothesis, the test statistic is χ^2-distributed with $(K-1)$ degrees of freedom (df) (Khan, 2020, p. 26). In addition, heterogeneity can be quantified with $I^2 = 100\% \cdot (Q - df)/Q$. This measurement lies between 0% and 100% and indicates the percentage of the between-study variance in the total variance (Higgins et al., 2003, p. 558).

3.2 Effect measures for continuous responses

The classical meta-analysis usually compares two groups: the experimental group (E) and the control group (C). In general, for a continuous outcome, the mean, the standard

deviation and the sample size are given for both groups (Schwarzer et al., 2015, p. 22). In all following calculations, $\bar{x}_E$, s_E, n_E denote the sample mean, standard deviation and sample size of the experimental group and $\bar{x}_C$, s_C, n_C denote the sample mean, standard deviation and sample size of the control group.

It is shown by Nakagawa et al. (2015) that the first approach to compare two means is the standardized mean difference (called Cohen's d) or the bias-corrected standardized mean difference (called Hedge's d). Cohen's d can be calculated using

$$d = \frac{\bar{x}_E - \bar{x}_C}{s_{\text{pooled}}}$$

with

$$s_{\text{pooled}} = \sqrt{\frac{(n_C - 1)\, s_C^2 + (n_E - 1)\, s_E^2}{n_C + n_E - 2}}.$$

For Hedge's d, the bias correction for small sample sizes $J = 1 - \frac{3}{4(n_C+n_E-2)-1}$ is added:

$$d = \frac{\bar{x}_E - \bar{x}_C}{s_{\text{pooled}}} J.$$

In both cases, the sampling variance s_d^2 is determined as follows:

$$s_d^2 = \frac{n_C + n_E}{n_C n_E} + \frac{d^2}{2\,(n_E + n_C)}.$$

As can be derived from the formulae, both measures depend also on the standard deviations of both groups. This problem does not appear with the response ratio $\ln \mathrm{RR}$. This is the natural logarithm of the ratio between the two means $\bar{x}_E$ and $\bar{x}_C$. Accordingly, the calculation is performed using

$$\ln \mathrm{RR} = \ln\left(\frac{\bar{x}_E}{\bar{x}_C}\right).$$

The corresponding sampling variance $s^2_{\ln \mathrm{RR}}$ is given by

$$s^2_{\ln \mathrm{RR}} = \frac{s_C^2}{n_C \bar{x}_C^2} + \frac{s_E^2}{n_E \bar{x}_E^2}.$$

Then, it was recognised that the difference of the standard deviations is also interesting, because these are also affected by treatments. The basis for this is provided by the unbiased estimator of the natural logarithm of the population standard deviation $\ln \sigma$. The estimation using the sampling standard deviation s can be expressed as

$$\ln \widehat{\sigma} = \ln s + \frac{1}{2\,(n-1)}$$

with related sampling variance

$$s^2_{\ln \widehat{\sigma}} = \frac{1}{2\,(n-1)}.$$

If sample size and σ are large enough, $\ln \sigma$ can be assumed to be normally distributed with variance $s^2_{\ln \sigma}$. Consequently, the variability ratio $\ln \mathrm{VR}$ – the natural logarithm of the ratio of the two standard deviations s_E and s_C – is given by

$$\ln \mathrm{VR} = \ln\left(\frac{s_E}{s_C}\right) + \frac{1}{2\,(n_E - 1)} - \frac{1}{2\,(n_C - 1)}.$$

The associated sampling variance can be expressed as

$$s^2_{\ln \mathrm{VR}} = \frac{1}{2\,(n_C - 1)} + \frac{1}{2\,(n_E - 1)}.$$

However, in the case of $\ln \mathrm{VR}$, the mean and variance are dependent on each other which can be problematic in some applications. This mean-variance relationship signifies that when $\bar{x}_E$ is larger than $\bar{x}_C$, s_E is larger than s_C in most cases, too. A more general approach was proposed by Nakagawa et al. (2015). The difference in variability can be also investigated using the coefficient of variation ratio $\ln \mathrm{CVR}$. This is the natural logarithm of the ratio between the two cofficients of variation $\mathrm{CV}_E = \frac{s_E}{\bar{x}_E}$ and $\mathrm{CV}_C = \frac{s_C}{\bar{x}_C}$. The $\ln \mathrm{CVR}$ and its sampling variance can be calculated using

$$\ln \mathrm{CVR} = \ln\left(\frac{\mathrm{CV}_E}{\mathrm{CV}_C}\right) + \frac{1}{2\,(n_E - 1)} - \frac{1}{2\,(n_C - 1)}$$

$$\begin{aligned} s^2_{\ln \mathrm{CVR}} = {} & \frac{s^2_C}{n_C \bar{x}^2_C} + \frac{1}{2\,(n_C - 1)} - 2\rho_{\ln \bar{x}^2_C,\, \ln s_C} \sqrt{\frac{s^2_C}{n_C \bar{x}^2_C} \frac{1}{2\,(n_C - 1)}} \\ & + \frac{s^2_E}{n_E \bar{x}^2_E} + \frac{1}{2\,(n_E - 1)} - 2\rho_{\ln \bar{x}^2_E,\, \ln s_E} \sqrt{\frac{s^2_E}{n_E \bar{x}^2_E} \frac{1}{2\,(n_E - 1)}}. \end{aligned}$$

$\rho_{\ln \bar{x}^2_C,\, \ln s_C}$ is the correlation between the means and standard deviations in the control group and $\rho_{\ln \bar{x}^2_E,\, \ln s_E}$ the correlation between the means and standard deviations in the experimental group. If the sample size is small enough, the correlations can be approximated by $\rho_{\ln \bar{x}^2_C,\, \ln s_C} = \rho_{\ln \bar{x}^2_E,\, \ln s_E}$. This means that a common correlation between all means and standard deviations can be estimated (Nakagawa et al., 2015, pp. 143-145).

4 Data set analysis

4.1 Purpose

The aim of the project is to quantify the potential of precision medicine in type 2 diabetes. The applied study design comes from the field of psychiatry. The idea is that a larger variance after treatment in the experimental group compared to the control group is an indicator of a heterogeneous treatment effect (Winkelbeiner et al., 2019, p. 1064). For this purpose, the project considers the CVR, the coefficient of variation ratio, of the HbA_{1c} level after treatment. If the coefficient is 1, the variability in the treatment and control group is equal. A coefficient smaller than 1 means that the variability in the control group is greater than in the treatment group. If the coefficient is greater than 1, the variability in the treatment group is greater than in the control group which indicates the presence of individual treatment responses. The size of the coefficient quantifies the magnitude of the potential of precision medicine (Winkelbeiner et al., 2019, p. 1064). A meta-analysis was conducted because estimating the overall effect is more precise than considering a single study (Haidich, 2010, p. 30). Only RCTs are included in the meta-analysis because they have a high level of evidence (Uetani et al., 2009, p. 307). This will help to determine whether the approach of precision medicine is appropriate in type 2 diabetes.

4.2 Data extraction and processing

The meta-analysis to be performed relies on the systematic reviews by Palmer et al. with 301 trials (Palmer et al., 2016, p. 313) and Tsapas et al. with 453 trials (Tsapas et al., 2020, p. 278). Therefore, only RCTs published in English are included. The German Diabetes Center has provided the relevant published papers and a table with the variables to be extracted for each study arm (experimental and control). The variables to be extracted have been:

- study id
- primary author of the study
- duration of the study

- drug and dosage
- size of the ITT-population
- number of participants who completed the study
- mean baseline characteristics
  - duration of diabetes [years]
  - age [years]
  - proportion of men [%]
  - body weight [kg]
  - BMI [kg/m^2]
  - mean $\mathrm{HbA_{1c}}$ level [%] at baseline incl. standard deviation, standard error
- mean $\mathrm{HbA_{1c}}$ level [%] after treatment incl. standard deviation, standard error, CI
- mean change in $\mathrm{HbA_{1c}}$ level [%] from baseline to the end of the study incl. least square variant, standard deviation, standard error, CI, p-value of a significance test
- mean change in $\mathrm{HbA_{1c}}$ level [%] after treatment adjusted for baseline values compared to placebo or comparator drug incl. least square variant, standard deviation, standard error, CI, p-value of a significance test

As some relevant information was not directly available in the desired form, some conversions were made.

Thus, in a few studies, the $\mathrm{HbA_{1c}}$ levels were only given in mmol/mol. However, since these were to be analysed on the %-scale, they were converted using the following formula (Weykamp, 2013, p. 396):

$$\mathrm{HbA_{1c}}[\%] = 0.0915 \cdot \mathrm{HbA_{1c}}[\mathrm{mmol/mol}] + 2.15.$$

In many cases, the median m, the IQR or the first quartile q_1 and third quartile q_3 were given. Then the mean $\bar{x}$ can be calculated using the following formula (Wan et al., 2014, p. 6):

$$\bar{x} \approx \frac{q_1 + m + q_3}{3}.$$

The associated standard deviation s can be calculated using this formula (Wan et al., 2014, p. 6):

$$s = \frac{q_3 - q_1}{2\Phi^{-1}\left(\frac{0.75n - 0.125}{n + 0.25}\right)}$$

with the number of study participants n and the cumulative distribution function of the standard normal distribution Φ.

Furthermore, the median m, the minimum min and maximum max are often given. Then the mean $\bar{x}$ is calculated using the following formula (Hozo et al., 2005, p. 8):

$$\bar{x} \approx \begin{cases} \frac{min+2m+max}{4} & n \leq 25, \\ m & n > 25 \end{cases}.$$

The associated standard deviation s can be calculated using this formula (Wan et al., 2014, p. 4):

$$s = \frac{max - min}{2\Phi^{-1}\left(\frac{n-0.375}{n+0.25}\right)}$$

with the number of study participants n and the cumulative distribution function of the standard normal distribution Φ.

Moreover, in some publications the standard error of the mean (SEM) was given. The conversion to the standard deviation s was done by the following equation (Koschack, 2008, p. 259):

$$SEM = \frac{s}{\sqrt{n}}.$$

If the lower and upper bound of a CI for the mean were given, the standard error and the standard deviation s could be determined. The $(1-\alpha)$ CI is given by

$$\left[\overline{x} - z_{1-\frac{\alpha}{2}}\frac{s}{\sqrt{n}},\ \overline{x} + z_{1-\frac{\alpha}{2}}\frac{s}{\sqrt{n}}\right]$$

with the $1-\frac{\alpha}{2}$ quantile of the standard normal distribution $z_{1-\frac{\alpha}{2}}$ and the number of study participants n. This calculation was made on the basis of a normal distribution assumption (Fahrmeir et al., 2016, pp. 358-359).

In some studies, the HbA_{1c} levels were examined at several points in time, for example as an interim report or by extending the study. In most cases, however, the number of participants who had taken part in the study up to this point was missing for these time points. In order to still be able to include the values in the analysis, the group size was interpolated or extrapolated via a linear regression model. For this purpose, a linear model of the form

$$y = \beta_0 + \beta_1 \cdot x_1 + \epsilon$$

is set up. y is the response variable, x_1 is the explanatory variable, β_0 and β_1 are the unknown parameters and ϵ the error term. The following assumptions are valid: $\mathrm{E}(\epsilon) = 0$, $\mathrm{Cov}(\epsilon) = \mathrm{E}(\epsilon\epsilon') = \sigma^2 I$ and $\epsilon \sim \mathcal{N}\left(0, \sigma^2 I\right)$ (Fahrmeir et al., 2013, pp. 73-77). In the present case, y is the number of participants in the study arm at the beginning of the study or the number of participants in the study arm who have completed the study at a specified time point. x is the given time point. If the number of subjects in

the study arm at the beginning of the study is considered, x is 0. Otherwise, x is the number of days, weeks or months at which the number of subjects in the study arm who have completed the study is given. With the help of this linear model, the values of y at different times x can now be predicted. In principle, the longest duration with the most information is included in the analysis.

4.3 Characteristics of included trials

After processing, the data set consists of 296 trials. This complies with 141 258 individual observations. All studies were published between 1987 and 2020. The median study duration is 24 weeks (IQR 24-28.25 weeks). The drugs in the treatment group were taken from ten different drug classes. The ten drug classes are: SGLT-2-Inhibitors, Metformin, DPP-4-Inhibitors/Gliptines, GLP-1-Receptor-Agonists, Thiazolidinediones/ Glitazones, Sulfonylureas, Alpha-Glucosidase-Inhibitors, Insulins, Combination and Others. Figure 4.1 represents the frequency of all drug classes.

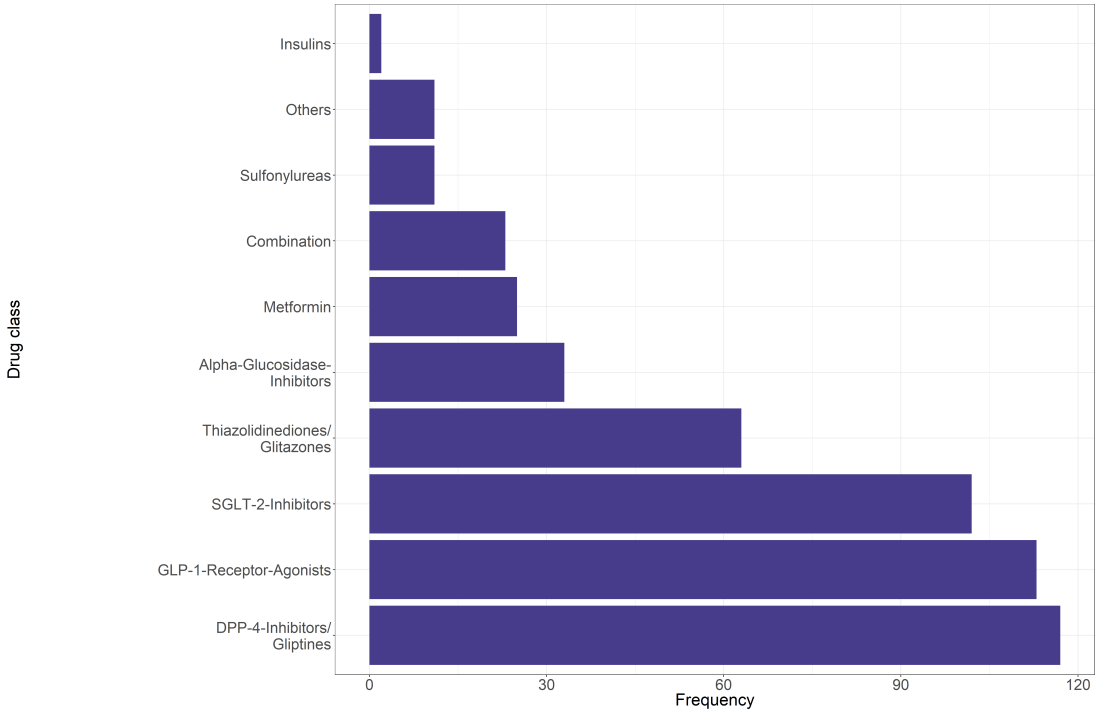

Figure 4.1: Frequency of drug classes in all trials. The y-axis indicates the ten drug classes, the x-axis the corresponding frequencies.

As can be seen in Figure 4.1, most of the drugs belong to the drug class DPP-4-Inhibitors/Gliptines and GLP-1-Receptor-Agonists. There are thus a total of 500 treatment groups. Furthermore, 303 placebo groups are available. Based on this, it

becomes clear that there are some studies with more than one treatment group.

Figure 4.2 illustrates the baseline characteristics of the study participants for the experimental and control groups separately. The baseline characteristics include the following variables: duration of diabetes, age, proportion of men, body weight, BMI and HbA_{1c} level at baseline.

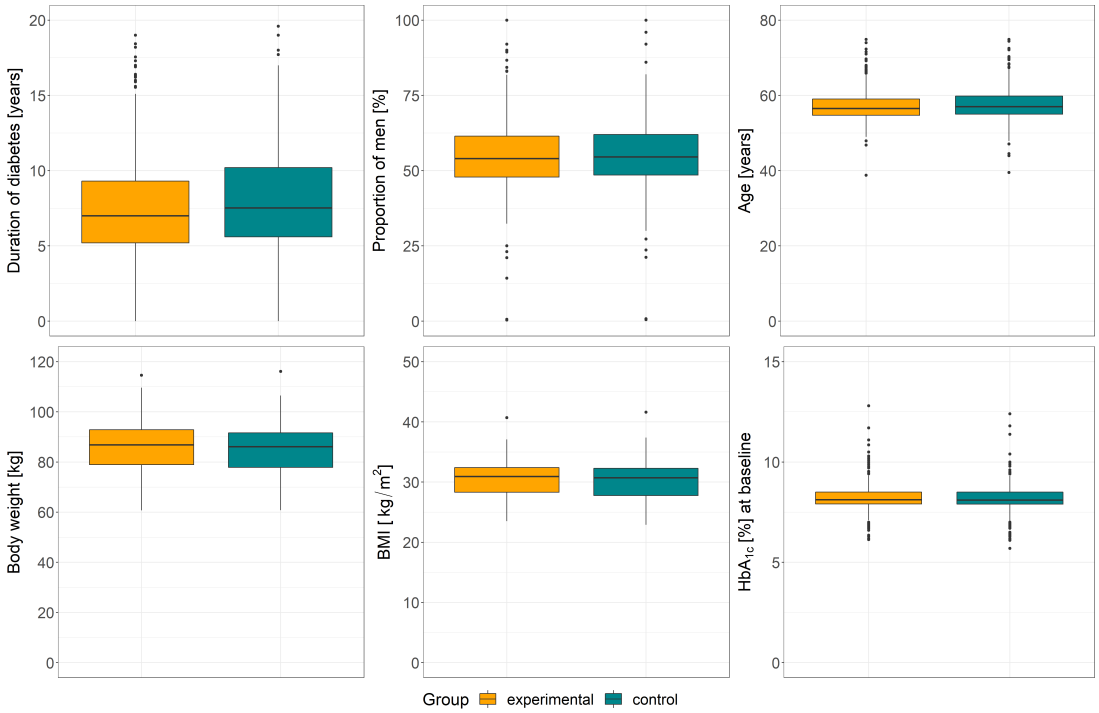

Figure 4.2: Representation of the six baseline characteristics: duration of diabetes, proportion of men, age, body weight, BMI and HbA_{1c} level at baseline. The orange boxes represent the experimental groups, the petrol boxes the control groups.

As Figure 4.2 underlines, the distribution of all variables in both groups is very similar. This results from the fact that only RCTs are included in the analysis. The median, the first quartile, the third quartile and the minimum and maximum are almost identical. A small exception is the duration of diabetes, where the values of the control group are generally higher. For the duration of diabetes, the minimum of both groups is 0, which means that there is at least one study in which the participants have been newly diagnosed with diabetes. For the proportion of men, the maximum of both groups is 100, which means that there is one study in which only men participated.

Figure 4.3 shows the mean values of the HbA_{1c} level after treatment incl. standard deviation separated by group.

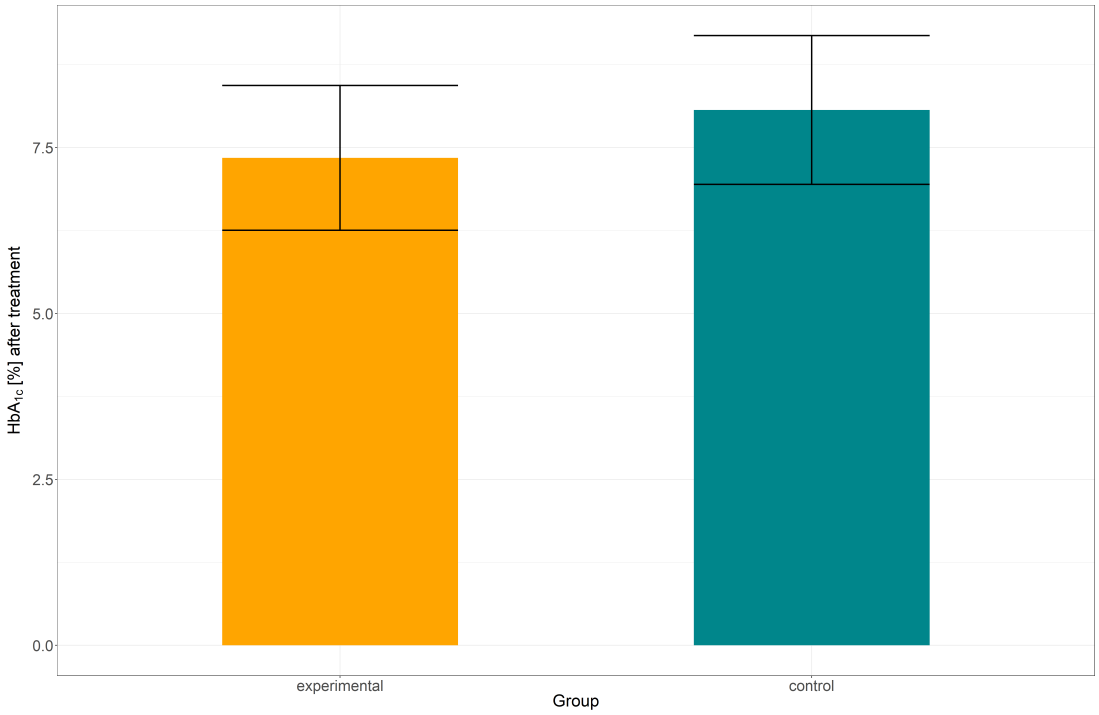

Figure 4.3: HbA_{1c} level after treatment incl. standard deviation. The orange bar represents the experimental group, the petrol bar the control group.

It is evident that the HbA_{1c} level after treatment is higher in the control group than in the experimental group. However, the standard deviations are comparable in both groups.

4.4 Meta-analysis

174 studies with 86 940 individual observations were eligible for the original meta-analysis. This corresponds to 272 pairwise comparisons. The effect size to be investigated in the meta-analysis was the $\ln \mathrm{CVR}$ of HbA_{1c} level after treatment. Accordingly, only studies for which the number of participants who completed the study and the HbA_{1c} level after treatment incl. standard deviation are available could be included.

The analysis was carried out in R (R Core Team, 2020) with the *metafor* package (Viechtbauer, 2010). A random effects model was applied to consider the between-study variation. Furthermore, the inverse variance method was used for weighting. The $\ln \mathrm{CVR}$ was calculated with the function *escalc*. However, it is assumed for the calculation that the data are normally distributed. Accordingly, the correlation terms are omitted from the calculation of the variance $s^2_{\ln \mathrm{CVR}}$, since mean and variance are independent in the case of normal distribution. Consequently, the following formula

was used to calculate the variance $s^2_{\ln \mathrm{CVR}}$:

$$s^2_{\ln \mathrm{CVR}} = \frac{s_C^2}{n_C \bar{x}_C^2} + \frac{1}{2\,(n_C - 1)} + \frac{s_E^2}{n_E \bar{x}_E^2} + \frac{1}{2\,(n_E - 1)}.$$

The results were also compared with the formulas with correlation terms. Since very similar results were obtained, the normal distribution assumption seems to be valid.

Figure 4.4 shows the forest plot of some example trials. The remaining forest plots can be found in the appendix.

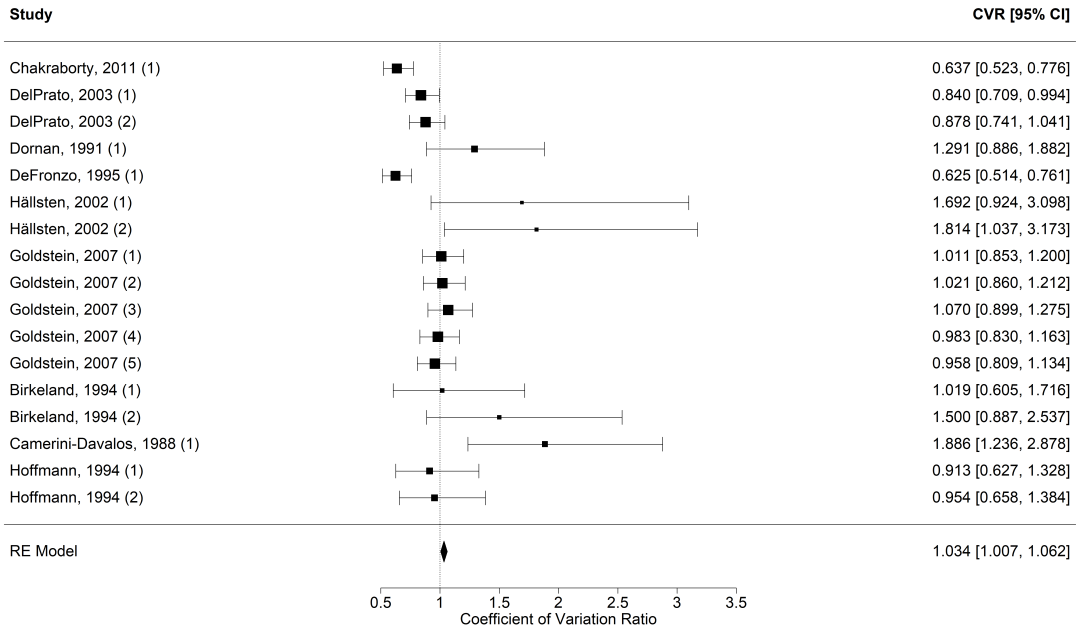

Figure 4.4: Forest plot of some example trials. The names of the trials can be read in the left column. The right column shows the CVR incl. 95% CI. In the middle, this is presented again graphically, with the area of the squares proportional to the weight. At the bottom the estimation of the random effects model incl. 95% CI is shown.

The CVR lies between 0.301 and 3.510. This wide range is already an indicator that the studies are heterogeneous. This is also confirmed by Cochran's Q test. The result $Q\,(df = 271) = 1769.7528$ with p-value < 0.0001 implied that there is heterogeneity between the studies. According to the $I^2 = 84.69\%$, heterogeneity is to be classified as high. This is because the studies are heterogeneous in terms of variance. This would have been expected and does not diminish results of the performed meta-analysis.

A funnel plot to control for publication bias is not necessary, as this has already been checked in the systematic reviews of Palmer et al. and Tsapas et al. In both cases, no

evidence for publication bias was found (Palmer et al., 2016, p. 320; Tsapas et al., 2020, p. 280).

When the CVR is 1, the variability in the treatment and control groups is equal. Consequently, with a CVR of 1.034, the variability in the treatment group is slightly higher than in the control group. Since the 95% CI ranges from 1.007 to 1.062 and the p-value is 0.0147, the result is statistically significant. However, the effect is that minimal that the result is not clinically relevant. Accordingly, in this case there is nearly no potential for precision medicine.

5 Discussion

The aim of the project was the quantification of the potential of precision medicine in type 2 diabetes. After data processing, a meta-analysis could be conducted. The most time-consuming part was the data extraction and processing.

The meta-analysis resulted in a CVR of 1.034 (95% CI 1.007 to 1.062). This implies that the variance in the treatment group is not considerably higher than in the control group. Accordingly, there is almost no potential for precision medicine in type 2 diabetes. Consequently, the treatment effect is constant, so that the occurrence of the average treatment effect can be assumed for all patients. The question of whether a treatment generally works can be investigated with the help of RCTs. The resulting estimated treatment effect is the average treatment effect (Winkelbeiner et al., 2019, p. 1064). So, in the future, research should be based on one treatment guideline for all patients.

There are some studies with more than one treatment group. In these cases, several treatment groups are accordingly compared with a common placebo group. For this purpose, it is assumed that these comparisons are independent of each other. But this assumption is not correct. Since several treatment groups are compared with a common control group in a study, one study provides several effect sizes for the meta-analysis. This leads to the fact that the effect sizes are correlated (Cooper et al., 2009, p. 358). An alternative approach to this classical meta-analysis is the network meta-analysis. It is an extension of the classical pairwise meta-analysis. Here, it is possible to compare more than two interventions directly or indirectly. This does not create the problem of placebo groups being counted more than once (Dias et al., 2019, p. F8).

Furthermore, there are some limitations of the ln CVR. Thus, the ln CVR can only be applied to ratio scaled data. Accordingly, the ln CVR cannot be used as an effect measure if this condition is not met. In addition, the ln CVR is based on the assumption that the standard deviation is proportional to the mean. But it is known that this assumption is not valid in many cases. An alternative approach is a random intercept and slope linear mixed-effects model. At this $\ln \widehat{\sigma}$ is the response and $\ln \bar{x}$ and group membership (control or treatment) are the explanatory variables. This results in the following model equation:

$$\ln \widehat{\sigma}_j = (\beta_0 + \tau_i) + (\beta_1 + \varphi_i)\, Group_j + \beta_2 \ln \bar{x}_j + \epsilon_j + m_j$$

with

$$\begin{pmatrix} \tau_i \\ \varphi_i \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_\tau^2 & \rho\sigma_\tau\sigma_\varphi \\ \rho\sigma_\tau\sigma_\varphi & \sigma_\varphi^2 \end{pmatrix} \right)$$

and

$$\epsilon_j \sim \mathcal{N}\left(0, \sigma_\epsilon^2\right)$$

and

$$m_j \sim \mathcal{N}\left(0, \sigma_{\ln \sigma_j}^2\right).$$

$j = 1, \ldots, n$ effect sizes from $i = 1, \ldots, K$ studies are included in the model. Accordingly, $\ln \widehat{\sigma}_j$ is the effect size j and $\ln \bar{x}_j$ is the mean estimate for the effect size *j*. *Group* is a dummy variable to represent group membership (controlgroup = 0 and treatmentgroup = 1). β_0 is the grand intercept and τ_i the deviation from β_0 for study *i*. β_1 is the grand slope and φ_i the deviation from β_1 for study *i*. β_2 is the regression coefficient for $\ln \bar{x}$. ϵ_j is the residual of effect size j and m_j is a sampling error effect for effect size j (Nakagawa et al., 2015, pp. 147-148).

The network meta-analysis and the random intercept and slope linear mixed-effects model can be carried out to verify the result from the conducted meta-analysis. Furthermore, the potential of precision medicine could be examined on the basis of other outcomes. This could be weight loss or fasting plasma glucose, for example. Moreover, a survival time analysis could also be implemented.

Based on the conducted meta-analysis, it can be concluded that the potential for precision medicine in type 2 diabetes is very low. This, of course, eliminates some of the hopes. However, other research approaches can now be focused on.

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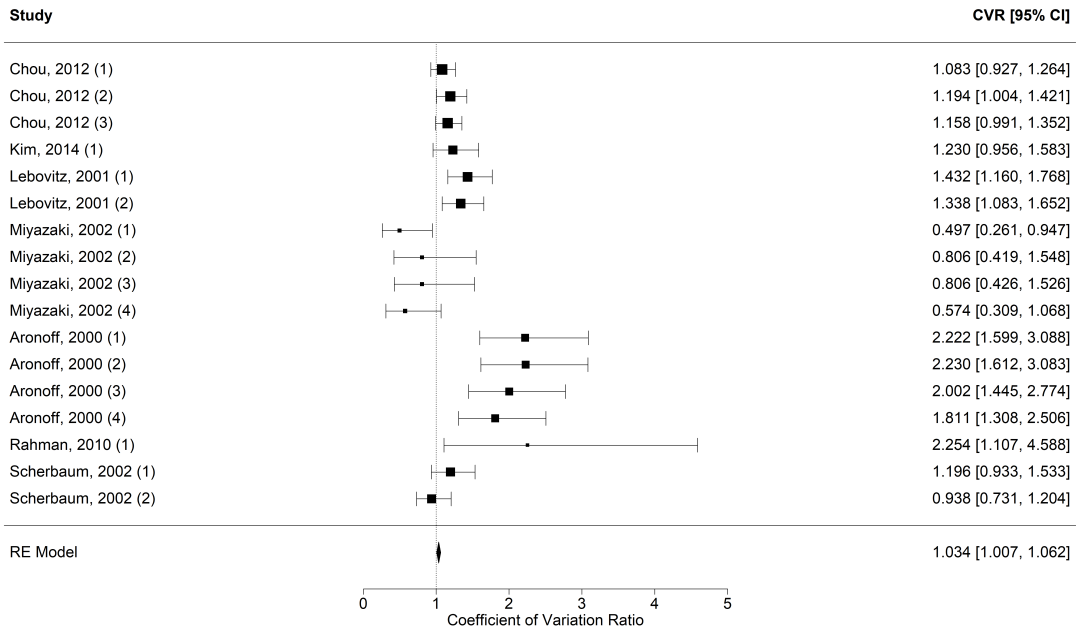
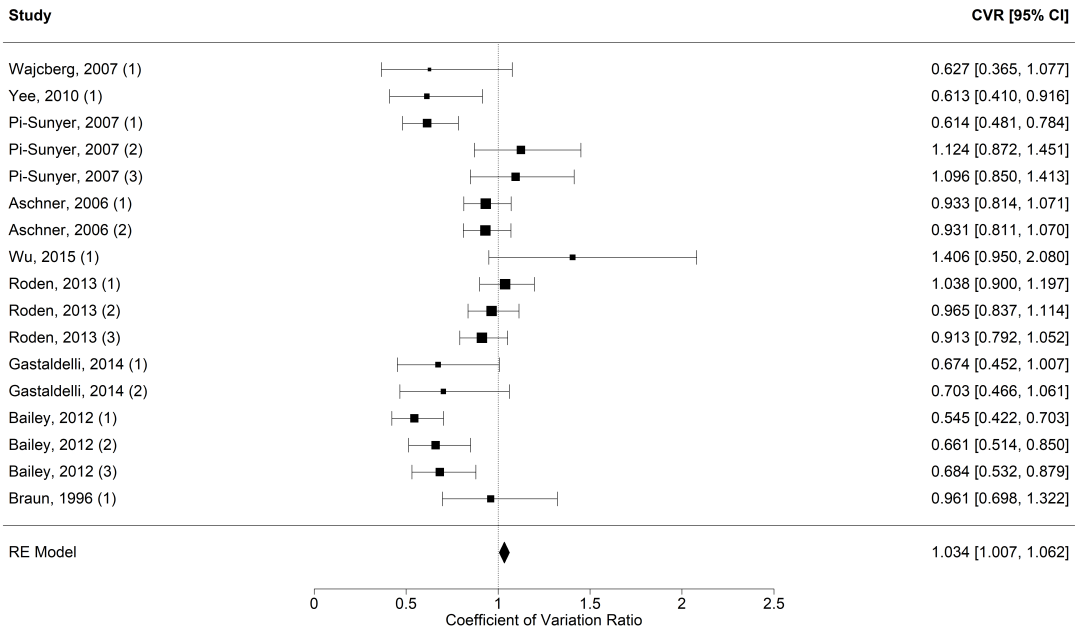
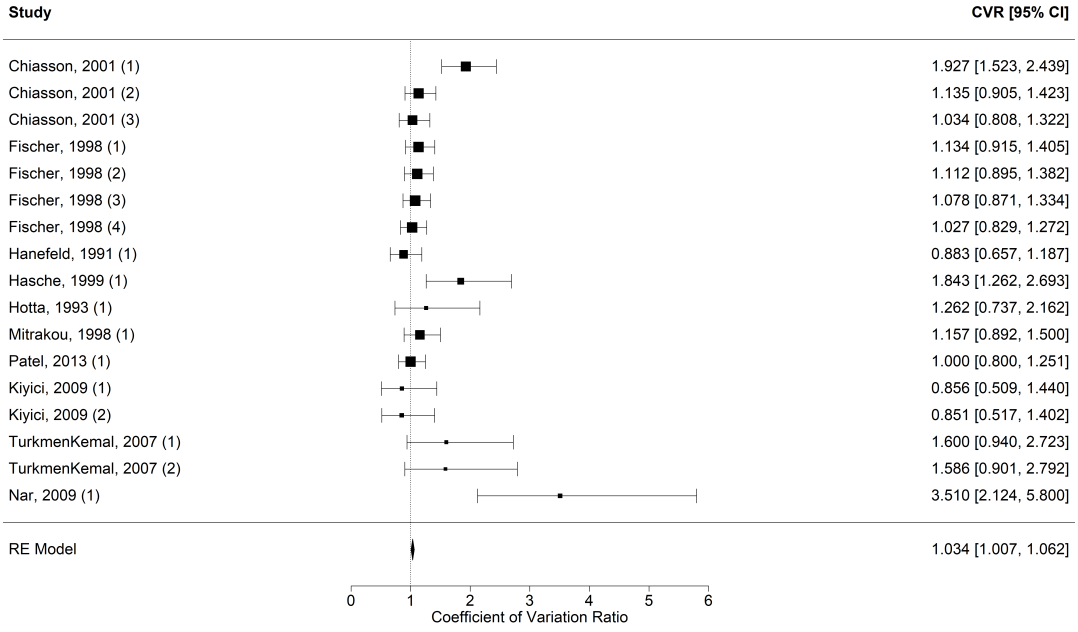
List of Figures

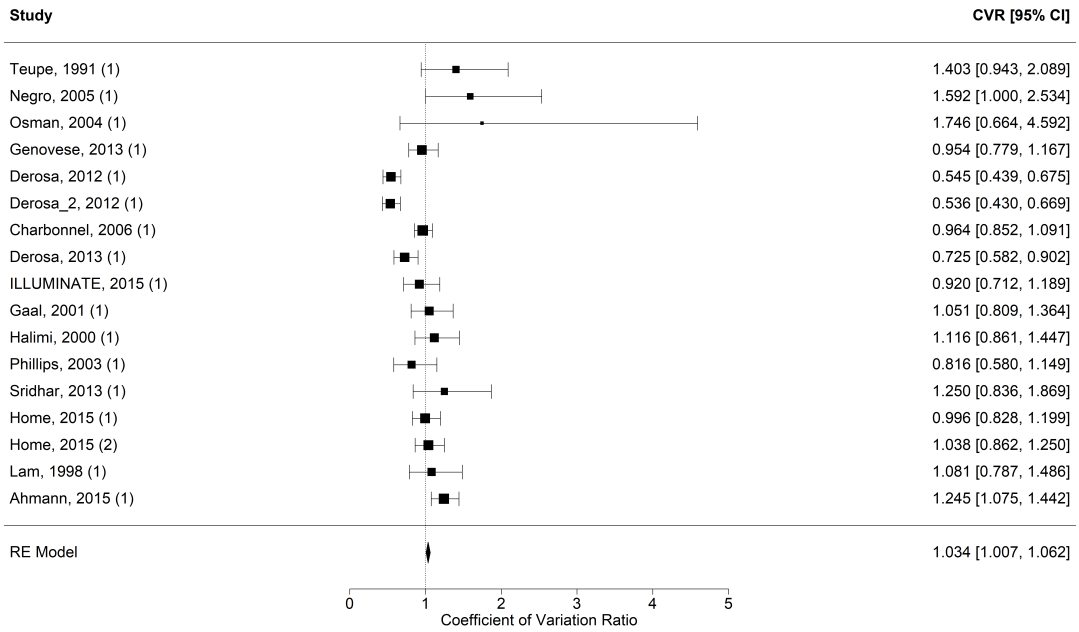
Appendix

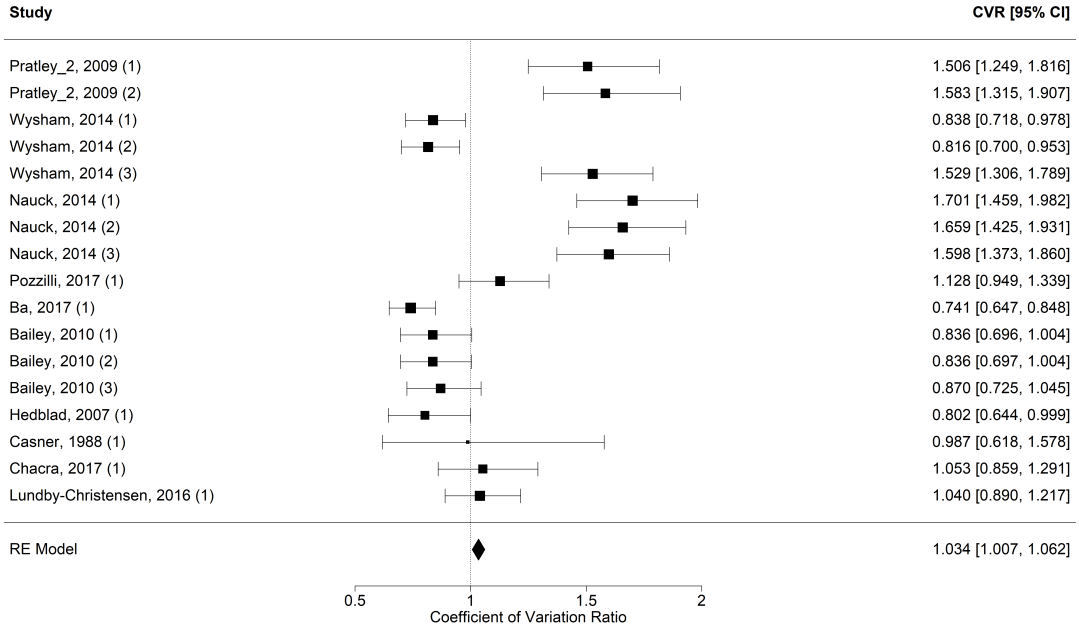
Forest plots

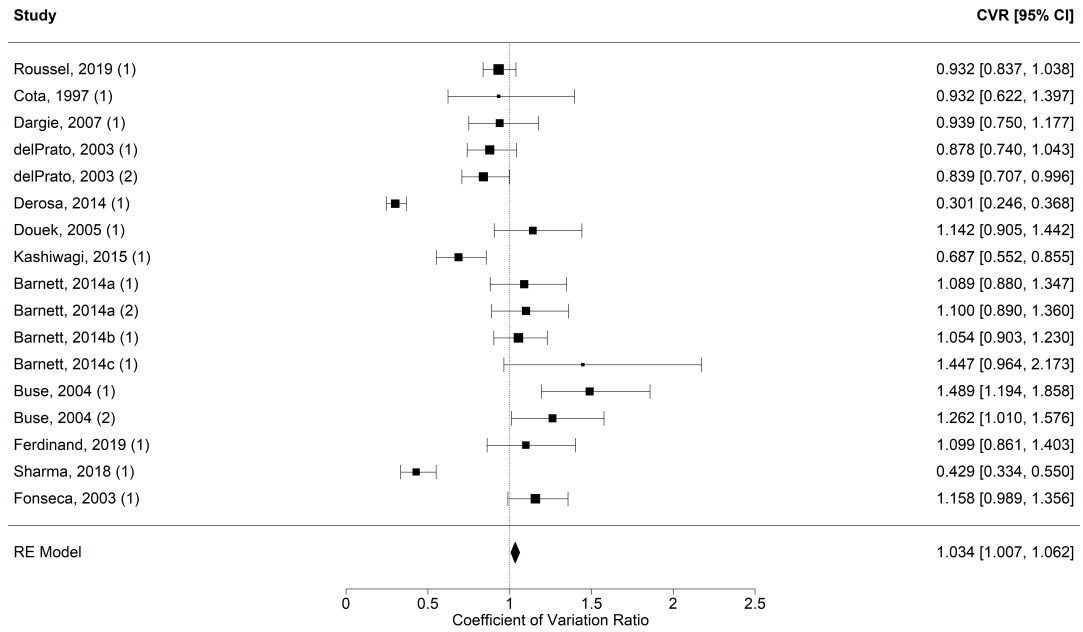


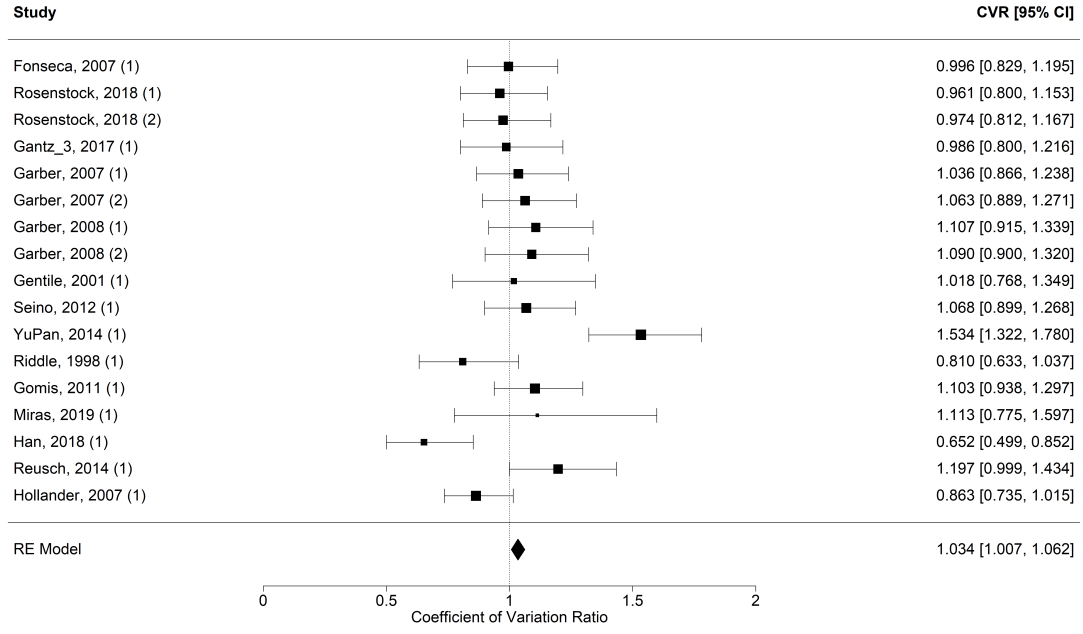

Study
CVR [95% CI]
Wajcberg, 2007 (1)
0.627 [0.365, 1.077]
Yee, 2010 (1)
0.613 [0.410, 0.916]
Pi-Sunyer, 2007 (1)
0.614 [0.481, 0.784]
Pi-Sunyer, 2007 (2)
1.124 [0.872, 1.451]
Pi-Sunyer, 2007 (3)
1.096 [0.850, 1.413]
Aschner, 2006 (1)
0.933 [0.814, 1.071]
Aschner, 2006 (2)
0.931 [0.811, 1.070]
Wu, 2015 (1)
1.406 [0.950, 2.080]
Roden, 2013 (1)
1.038 [0.900, 1.197]
Roden, 2013 (2)
0.965 [0.837, 1.114]
Roden, 2013 (3)
0.913 [0.792, 1.052]
Gastaldelli, 2014 (1)
0.674 [0.452, 1.007]
Gastaldelli, 2014 (2)
0.703 [0.466, 1.061]
Bailey, 2012 (1)
0.545 [0.422, 0.703]
Bailey, 2012 (2)
0.661 [0.514, 0.850]
Bailey, 2012 (3)
0.684 [0.532, 0.879]
Braun, 1996 (1)
0.961 [0.698, 1.322]
RE Model
1.034 [1.007, 1.062]
0
0.5
1
1.5
2
2.5
Coefficient of Variation Ratio

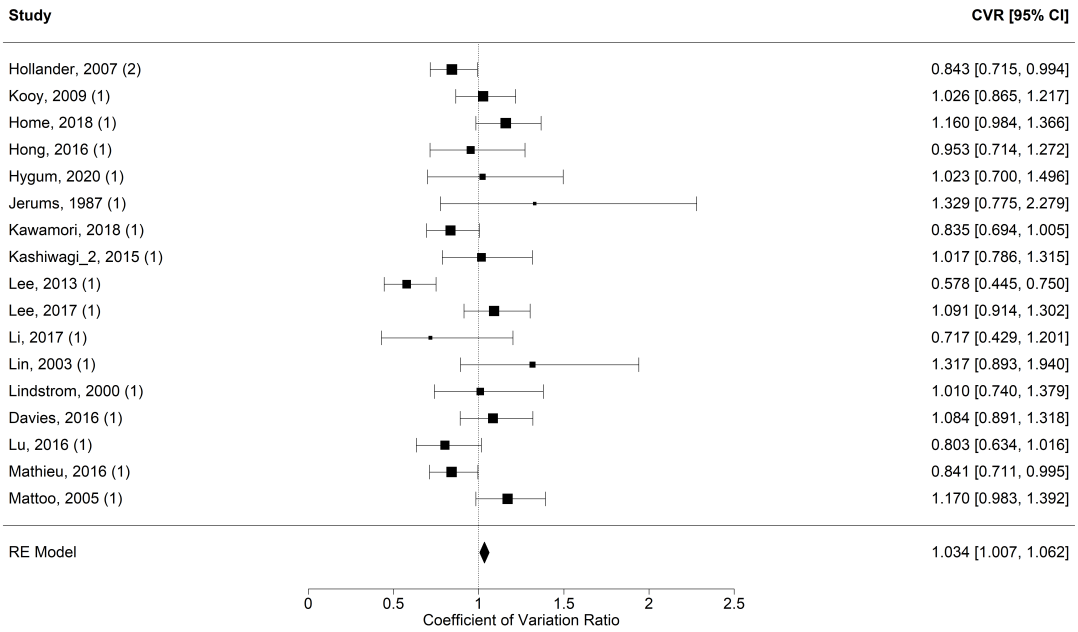

Study
CVR [95% CI]
Chiasson, 2001 (1)
1.927 [1.523, 2.439]
Chiasson, 2001 (2)
1.135 [0.905, 1.423]
Chiasson, 2001 (3)
1.034 [0.808, 1.322]
Fischer, 1998 (1)
1.134 [0.915, 1.405]
Fischer, 1998 (2)
1.112 [0.895, 1.382]
Fischer, 1998 (3)
1.078 [0.871, 1.334]
Fischer, 1998 (4)
1.027 [0.829, 1.272]
Hanefeld, 1991 (1)
0.883 [0.657, 1.187]
Hasche, 1999 (1)
1.843 [1.262, 2.693]
Hotta, 1993 (1)
1.262 [0.737, 2.162]
Mitrakou, 1998 (1)
1.157 [0.892, 1.500]
Patel, 2013 (1)
1.000 [0.800, 1.251]
Kiyici, 2009 (1)
0.856 [0.509, 1.440]
Kiyici, 2009 (2)
0.851 [0.517, 1.402]
TurkmenKemal, 2007 (1)
1.600 [0.940, 2.723]
TurkmenKemal, 2007 (2)
1.586 [0.901, 2.792]
Nar, 2009 (1)
3.510 [2.124, 5.800]
RE Model
1.034 [1.007, 1.062]
0
1
2
3
4
5
6
Coefficient of Variation Ratio

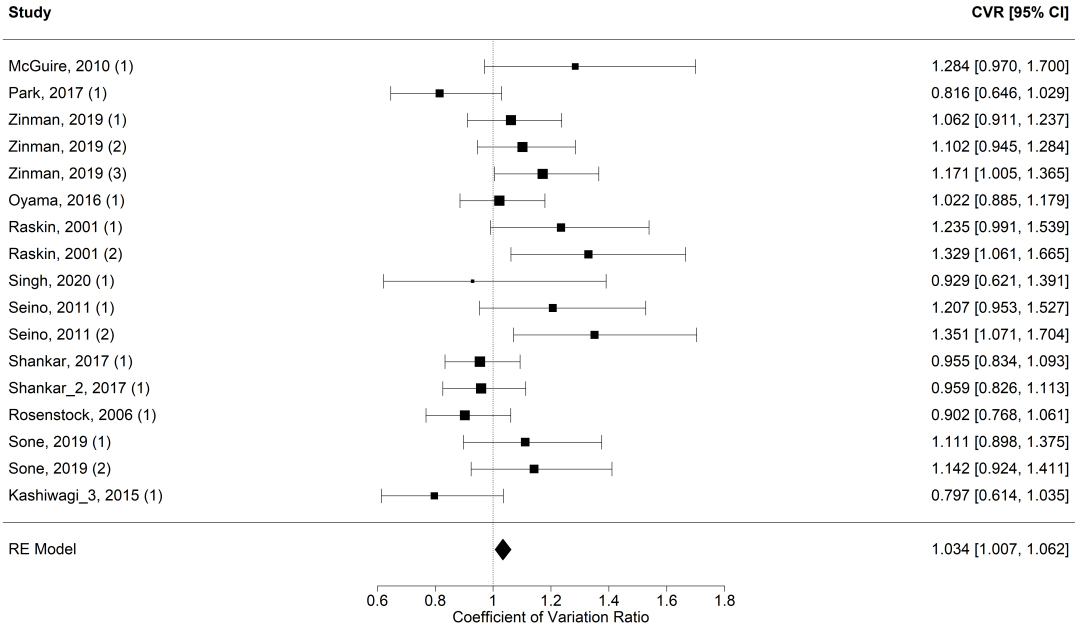

Study
CVR [95% CI]
Teupe, 1991 (1)
1.403 [0.943, 2.089]
Negro, 2005 (1)
1.592 [1.000, 2.534]
Osman, 2004 (1)
1.746 [0.664, 4.592]
Genovese, 2013 (1)
0.954 [0.779, 1.167]
Derosa, 2012 (1)
0.545 [0.439, 0.675]
Derosa_2, 2012 (1)
0.536 [0.430, 0.669]
Charbonnel, 2006 (1)
0.964 [0.852, 1.091]
Derosa, 2013 (1)
0.725 [0.582, 0.902]
ILLUMINATE, 2015 (1)
0.920 [0.712, 1.189]
Gaal, 2001 (1)
1.051 [0.809, 1.364]
Halimi, 2000 (1)
1.116 [0.861, 1.447]
Phillips, 2003 (1)
0.816 [0.580, 1.149]
Sridhar, 2013 (1)
1.250 [0.836, 1.869]
Home, 2015 (1)
0.996 [0.828, 1.199]
Home, 2015 (2)
1.038 [0.862, 1.250]
Lam, 1998 (1)
1.081 [0.787, 1.486]
Ahmann, 2015 (1)
1.245 [1.075, 1.442]
RE Model
1.034 [1.007, 1.062]
0
1
2
3
4
5
Coefficient of Variation Ratio

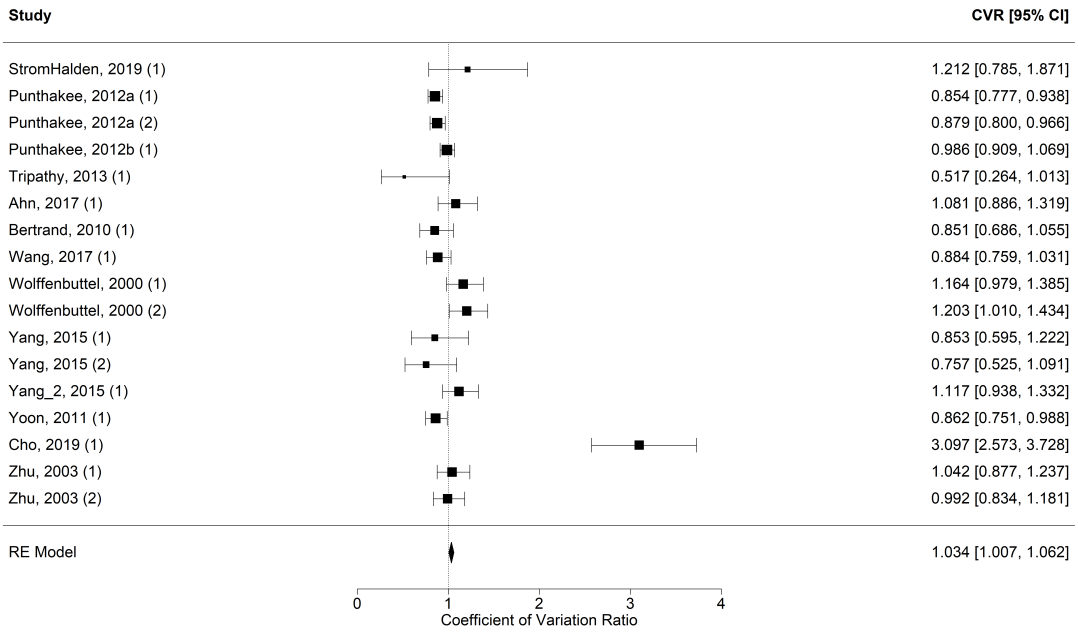

Study
CVR [95% CI]
Pratley_2, 2009 (1)
1.506 [1.249, 1.816]
Pratley_2, 2009 (2)
1.583 [1.315, 1.907]
Wysham, 2014 (1)
0.838 [0.718, 0.978]
Wysham, 2014 (2)
0.816 [0.700, 0.953]
Wysham, 2014 (3)
1.529 [1.306, 1.789]
Nauck, 2014 (1)
1.701 [1.459, 1.982]
Nauck, 2014 (2)
1.659 [1.425, 1.931]
Nauck, 2014 (3)
1.598 [1.373, 1.860]
Pozzilli, 2017 (1)
1.128 [0.949, 1.339]
Ba, 2017 (1)
0.741 [0.647, 0.848]
Bailey, 2010 (1)
0.836 [0.696, 1.004]
Bailey, 2010 (2)
0.836 [0.697, 1.004]
Bailey, 2010 (3)
0.870 [0.725, 1.045]
Hedblad, 2007 (1)
0.802 [0.644, 0.999]
Casner, 1988 (1)
0.987 [0.618, 1.578]
Chacra, 2017 (1)
1.053 [0.859, 1.291]
Lundby-Christensen, 2016 (1)
1.040 [0.890, 1.217]
RE Model
1.034 [1.007, 1.062]
0.5
1
1.5
2
Coefficient of Variation Ratio

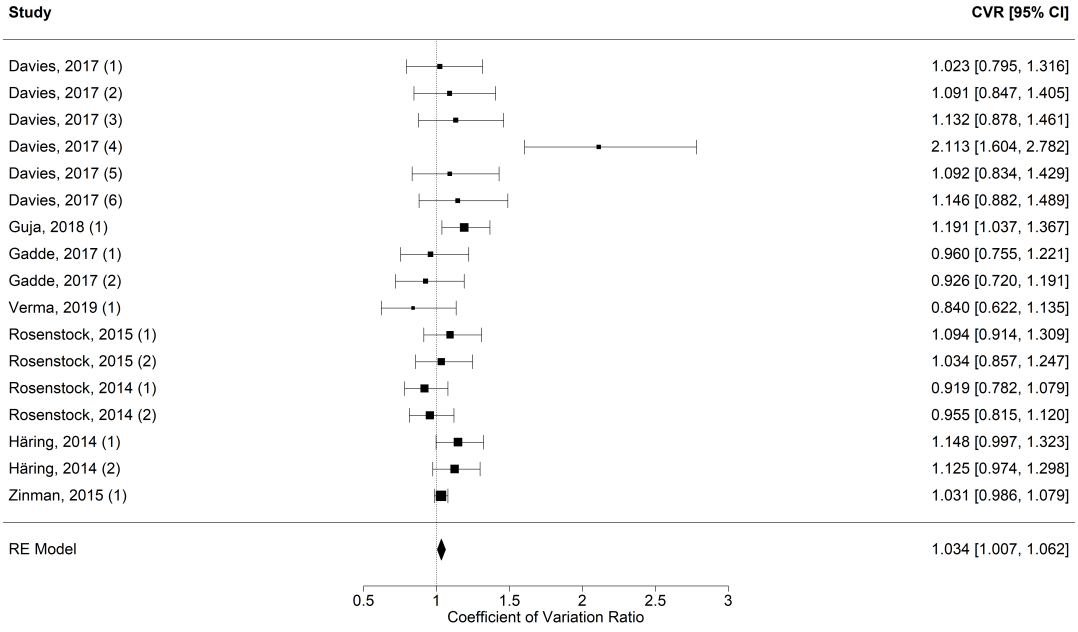

Study
CVR [95% CI]
Roussel, 2019 (1)
0.932 [0.837, 1.038]
Cota, 1997 (1)
0.932 [0.622, 1.397]
Dargie, 2007 (1)
0.939 [0.750, 1.177]
delPrato, 2003 (1)
0.878 [0.740, 1.043]
delPrato, 2003 (2)
0.839 [0.707, 0.996]
Derosa, 2014 (1)
0.301 [0.246, 0.368]
Douek, 2005 (1)
1.142 [0.905, 1.442]
Kashiwagi, 2015 (1)
0.687 [0.552, 0.855]
Barnett, 2014a (1)
1.089 [0.880, 1.347]
Barnett, 2014a (2)
1.100 [0.890, 1.360]
Barnett, 2014b (1)
1.054 [0.903, 1.230]
Barnett, 2014c (1)
1.447 [0.964, 2.173]
Buse, 2004 (1)
1.489 [1.194, 1.858]
Buse, 2004 (2)
1.262 [1.010, 1.576]
Ferdinand, 2019 (1)
1.099 [0.861, 1.403]
Sharma, 2018 (1)
0.429 [0.334, 0.550]
Fonseca, 2003 (1)
1.158 [0.989, 1.356]
RE Model
1.034 [1.007, 1.062]
0
0.5
1
1.5
2
2.5
Coefficient of Variation Ratio

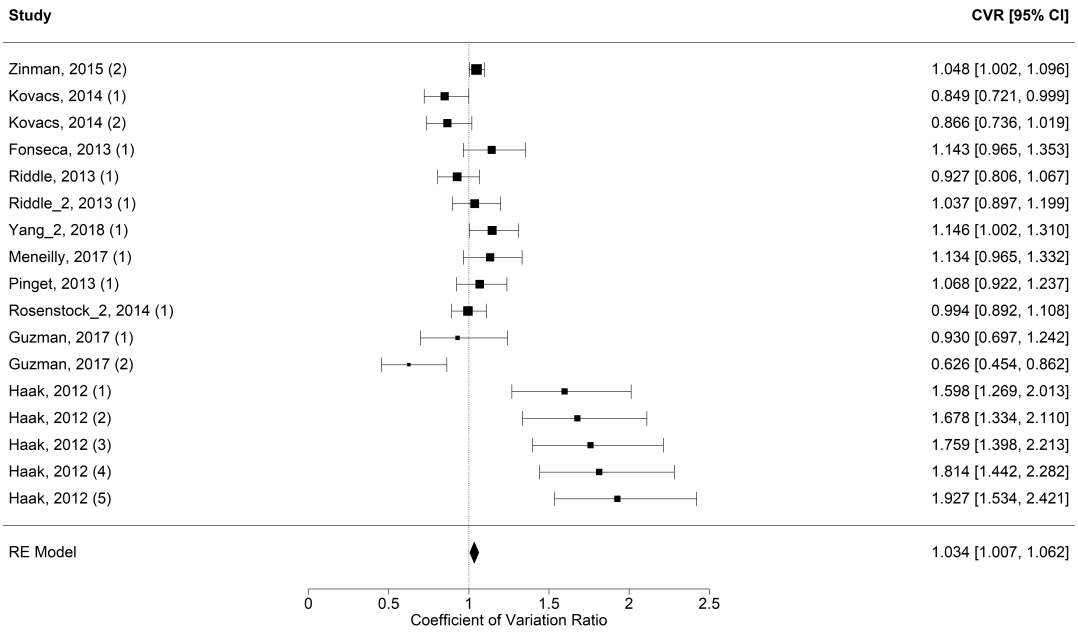

Study
CVR [95% CI]
Fonseca, 2007 (1)
0.996 [0.829, 1.195]
Rosenstock, 2018 (1)
0.961 [0.800, 1.153]
Rosenstock, 2018 (2)
0.974 [0.812, 1.167]
Gantz_3, 2017 (1)
0.986 [0.800, 1.216]
Garber, 2007 (1)
1.036 [0.866, 1.238]
Garber, 2007 (2)
1.063 [0.889, 1.271]
Garber, 2008 (1)
1.107 [0.915, 1.339]
Garber, 2008 (2)
1.090 [0.900, 1.320]
Gentile, 2001 (1)
1.018 [0.768, 1.349]
Seino, 2012 (1)
1.068 [0.899, 1.268]
YuPan, 2014 (1)
1.534 [1.322, 1.780]
Riddle, 1998 (1)
0.810 [0.633, 1.037]
Gomis, 2011 (1)
1.103 [0.938, 1.297]
Miras, 2019 (1)
1.113 [0.775, 1.597]
Han, 2018 (1)
0.652 [0.499, 0.852]
Reusch, 2014 (1)
1.197 [0.999, 1.434]
Hollander, 2007 (1)
0.863 [0.735, 1.015]
RE Model
1.034 [1.007, 1.062]
0
0.5
1
1.5
2
Coefficient of Variation Ratio

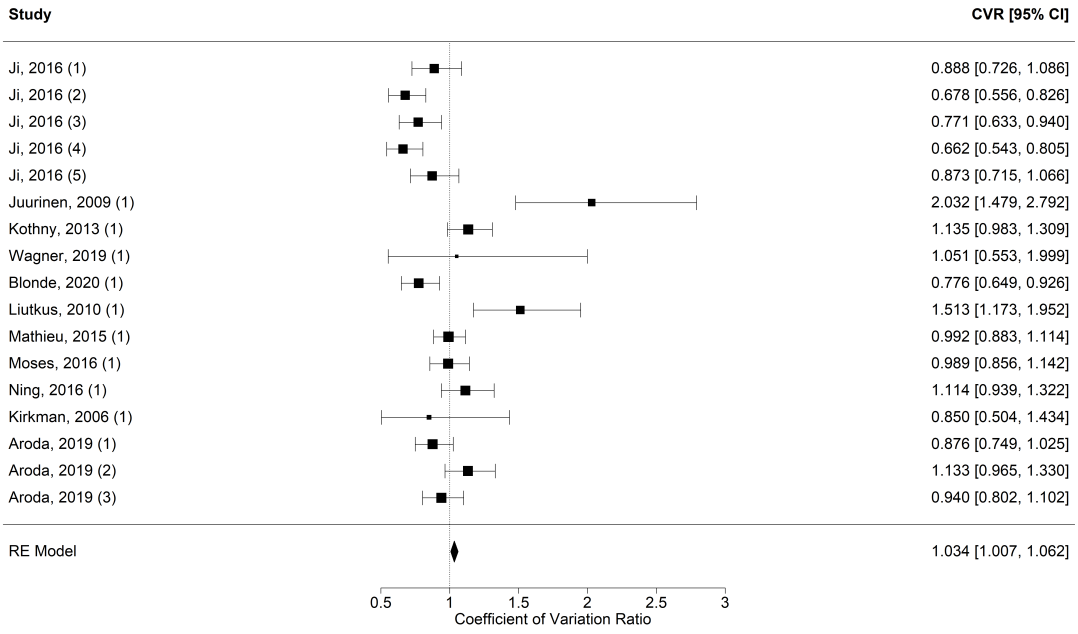

Study
CVR [95% CI]
Hollander, 2007 (2)
0.843 [0.715, 0.994]
Kooy, 2009 (1)
1.026 [0.865, 1.217]
Home, 2018 (1)
1.160 [0.984, 1.366]
Hong, 2016 (1)
0.953 [0.714, 1.272]
Hygum, 2020 (1)
1.023 [0.700, 1.496]
Jerums, 1987 (1)
1.329 [0.775, 2.279]
Kawamori, 2018 (1)
0.835 [0.694, 1.005]
Kashiwagi_2, 2015 (1)
1.017 [0.786, 1.315]
Lee, 2013 (1)
0.578 [0.445, 0.750]
Lee, 2017 (1)
1.091 [0.914, 1.302]
Li, 2017 (1)
0.717 [0.429, 1.201]
Lin, 2003 (1)
1.317 [0.893, 1.940]
Lindstrom, 2000 (1)
1.010 [0.740, 1.379]
Davies, 2016 (1)
1.084 [0.891, 1.318]
Lu, 2016 (1)
0.803 [0.634, 1.016]
Mathieu, 2016 (1)
0.841 [0.711, 0.995]
Mattoo, 2005 (1)
1.170 [0.983, 1.392]
RE Model
1.034 [1.007, 1.062]
0
0.5
1
1.5
2
2.5
Coefficient of Variation Ratio

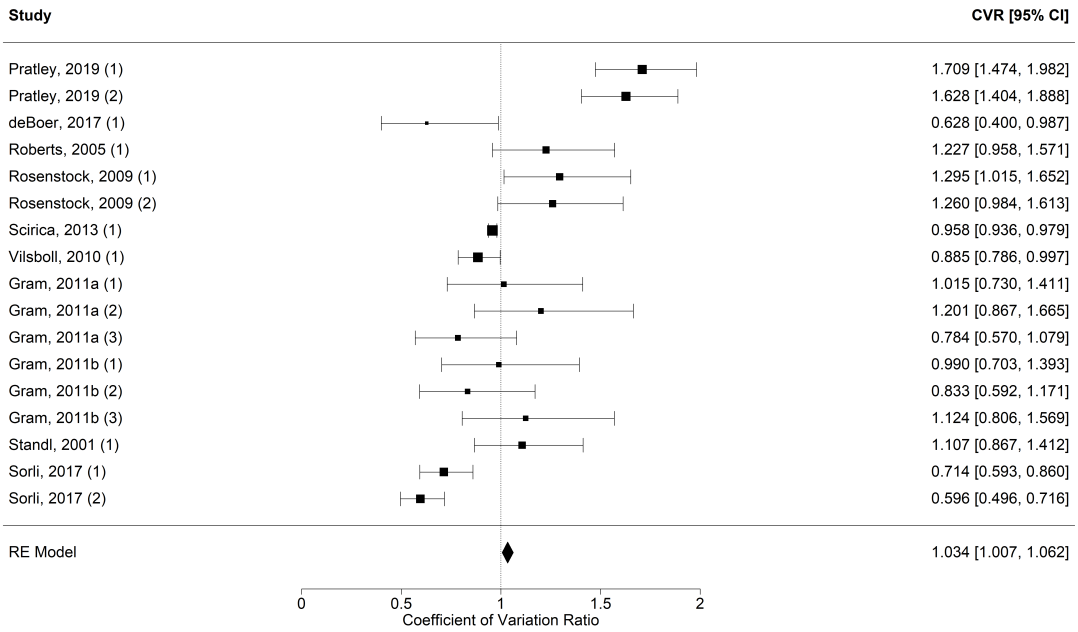

Study
CVR [95% CI]
McGuire, 2010 (1)
1.284 [0.970, 1.700]
Park, 2017 (1)
0.816 [0.646, 1.029]
Zinman, 2019 (1)
1.062 [0.911, 1.237]
Zinman, 2019 (2)
1.102 [0.945, 1.284]
Zinman, 2019 (3)
1.171 [1.005, 1.365]
Oyama, 2016 (1)
1.022 [0.885, 1.179]
Raskin, 2001 (1)
1.235 [0.991, 1.539]
Raskin, 2001 (2)
1.329 [1.061, 1.665]
Singh, 2020 (1)
0.929 [0.621, 1.391]
Seino, 2011 (1)
1.207 [0.953, 1.527]
Seino, 2011 (2)
1.351 [1.071, 1.704]
Shankar, 2017 (1)
0.955 [0.834, 1.093]
Shankar_2, 2017 (1)
0.959 [0.826, 1.113]
Rosenstock, 2006 (1)
0.902 [0.768, 1.061]
Sone, 2019 (1)
1.111 [0.898, 1.375]
Sone, 2019 (2)
1.142 [0.924, 1.411]
Kashiwagi_3, 2015 (1)
0.797 [0.614, 1.035]
RE Model
1.034 [1.007, 1.062]
0.6
0.8
1
1.2
1.4
1.6
1.8
Coefficient of Variation Ratio

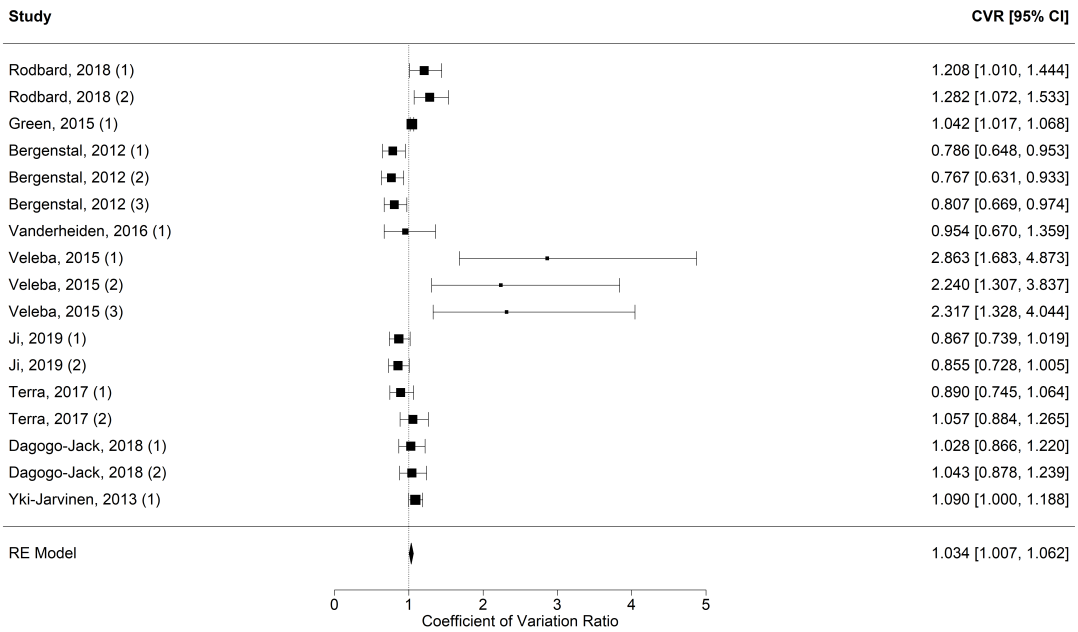

Study
CVR [95% CI]
StromHalden, 2019 (1)
1.212 [0.785, 1.871]
Punthakee, 2012a (1)
0.854 [0.777, 0.938]
Punthakee, 2012a (2)
0.879 [0.800, 0.966]
Punthakee, 2012b (1)
0.986 [0.909, 1.069]
Tripathy, 2013 (1)
0.517 [0.264, 1.013]
Ahn, 2017 (1)
1.081 [0.886, 1.319]
Bertrand, 2010 (1)
0.851 [0.686, 1.055]
Wang, 2017 (1)
0.884 [0.759, 1.031]
Wolffenbuttel, 2000 (1)
1.164 [0.979, 1.385]
Wolffenbuttel, 2000 (2)
1.203 [1.010, 1.434]
Yang, 2015 (1)
0.853 [0.595, 1.222]
Yang, 2015 (2)
0.757 [0.525, 1.091]
Yang_2, 2015 (1)
1.117 [0.938, 1.332]
Yoon, 2011 (1)
0.862 [0.751, 0.988]
Cho, 2019 (1)
3.097 [2.573, 3.728]
Zhu, 2003 (1)
1.042 [0.877, 1.237]
Zhu, 2003 (2)
0.992 [0.834, 1.181]
RE Model
1.034 [1.007, 1.062]
0
1
2
3
4
Coefficient of Variation Ratio


Study
CVR [95% CI]
Davies, 2017 (1)
1.023 [0.795, 1.316]
Davies, 2017 (2)
1.091 [0.847, 1.405]
Davies, 2017 (3)
1.132 [0.878, 1.461]
Davies, 2017 (4)
2.113 [1.604, 2.782]
Davies, 2017 (5)
1.092 [0.834, 1.429]
Davies, 2017 (6)
1.146 [0.882, 1.489]
Guja, 2018 (1)
1.191 [1.037, 1.367]
Gadde, 2017 (1)
0.960 [0.755, 1.221]
Gadde, 2017 (2)
0.926 [0.720, 1.191]
Verma, 2019 (1)
0.840 [0.622, 1.135]
Rosenstock, 2015 (1)
1.094 [0.914, 1.309]
Rosenstock, 2015 (2)
1.034 [0.857, 1.247]
Rosenstock, 2014 (1)
0.919 [0.782, 1.079]
Rosenstock, 2014 (2)
0.955 [0.815, 1.120]
Häring, 2014 (1)
1.148 [0.997, 1.323]
Häring, 2014 (2)
1.125 [0.974, 1.298]
Zinman, 2015 (1)
1.031 [0.986, 1.079]
RE Model
1.034 [1.007, 1.062]
0.5
1
1.5
2
2.5
3
Coefficient of Variation Ratio


Study
CVR [95% CI]
Zinman, 2015 (2)
1.048 [1.002, 1.096]
Kovacs, 2014 (1)
0.849 [0.721, 0.999]
Kovacs, 2014 (2)
0.866 [0.736, 1.019]
Fonseca, 2013 (1)
1.143 [0.965, 1.353]
Riddle, 2013 (1)
0.927 [0.806, 1.067]
Riddle_2, 2013 (1)
1.037 [0.897, 1.199]
Yang_2, 2018 (1)
1.146 [1.002, 1.310]
Meneilly, 2017 (1)
1.134 [0.965, 1.332]
Pinget, 2013 (1)
1.068 [0.922, 1.237]
Rosenstock_2, 2014 (1)
0.994 [0.892, 1.108]
Guzman, 2017 (1)
0.930 [0.697, 1.242]
Guzman, 2017 (2)
0.626 [0.454, 0.862]
Haak, 2012 (1)
1.598 [1.269, 2.013]
Haak, 2012 (2)
1.678 [1.334, 2.110]
Haak, 2012 (3)
1.759 [1.398, 2.213]
Haak, 2012 (4)
1.814 [1.442, 2.282]
Haak, 2012 (5)
1.927 [1.534, 2.421]
RE Model
1.034 [1.007, 1.062]
0
0.5
1
1.5
2
2.5
Coefficient of Variation Ratio


Study
CVR [95% CI]
Ji, 2016 (1)
0.888 [0.726, 1.086]
Ji, 2016 (2)
0.678 [0.556, 0.826]
Ji, 2016 (3)
0.771 [0.633, 0.940]
Ji, 2016 (4)
0.662 [0.543, 0.805]
Ji, 2016 (5)
0.873 [0.715, 1.066]
Juurinen, 2009 (1)
2.032 [1.479, 2.792]
Kothny, 2013 (1)
1.135 [0.983, 1.309]
Wagner, 2019 (1)
1.051 [0.553, 1.999]
Blonde, 2020 (1)
0.776 [0.649, 0.926]
Liutkus, 2010 (1)
1.513 [1.173, 1.952]
Mathieu, 2015 (1)
0.992 [0.883, 1.114]
Moses, 2016 (1)
0.989 [0.856, 1.142]
Ning, 2016 (1)
1.114 [0.939, 1.322]
Kirkman, 2006 (1)
0.850 [0.504, 1.434]
Aroda, 2019 (1)
0.876 [0.749, 1.025]
Aroda, 2019 (2)
1.133 [0.965, 1.330]
Aroda, 2019 (3)
0.940 [0.802, 1.102]
RE Model
1.034 [1.007, 1.062]
0.5
1
1.5
2
2.5
3
Coefficient of Variation Ratio


Study
CVR [95% CI]
Pratley, 2019 (1)
1.709 [1.474, 1.982]
Pratley, 2019 (2)
1.628 [1.404, 1.888]
deBoer, 2017 (1)
0.628 [0.400, 0.987]
Roberts, 2005 (1)
1.227 [0.958, 1.571]
Rosenstock, 2009 (1)
1.295 [1.015, 1.652]
Rosenstock, 2009 (2)
1.260 [0.984, 1.613]
Scirica, 2013 (1)
0.958 [0.936, 0.979]
Vilsboll, 2010 (1)
0.885 [0.786, 0.997]
Gram, 2011a (1)
1.015 [0.730, 1.411]
Gram, 2011a (2)
1.201 [0.867, 1.665]
Gram, 2011a (3)
0.784 [0.570, 1.079]
Gram, 2011b (1)
0.990 [0.703, 1.393]
Gram, 2011b (2)
0.833 [0.592, 1.171]
Gram, 2011b (3)
1.124 [0.806, 1.569]
Standl, 2001 (1)
1.107 [0.867, 1.412]
Sorli, 2017 (1)
0.714 [0.593, 0.860]
Sorli, 2017 (2)
0.596 [0.496, 0.716]
RE Model
1.034 [1.007, 1.062]
0
0.5
1
1.5
2
Coefficient of Variation Ratio


Study
CVR [95% CI]
Rodbard, 2018 (1)
1.208 [1.010, 1.444]
Rodbard, 2018 (2)
1.282 [1.072, 1.533]
Green, 2015 (1)
1.042 [1.017, 1.068]
Bergenstal, 2012 (1)
0.786 [0.648, 0.953]
Bergenstal, 2012 (2)
0.767 [0.631, 0.933]
Bergenstal, 2012 (3)
0.807 [0.669, 0.974]
Vanderheiden, 2016 (1)
0.954 [0.670, 1.359]
Veleba, 2015 (1)
2.863 [1.683, 4.873]
Veleba, 2015 (2)
2.240 [1.307, 3.837]
Veleba, 2015 (3)
2.317 [1.328, 4.044]
Ji, 2019 (1)
0.867 [0.739, 1.019]
Ji, 2019 (2)
0.855 [0.728, 1.005]
Terra, 2017 (1)
0.890 [0.745, 1.064]
Terra, 2017 (2)
1.057 [0.884, 1.265]
Dagogo-Jack, 2018 (1)
1.028 [0.866, 1.220]
Dagogo-Jack, 2018 (2)
1.043 [0.878, 1.239]
Yki-Jarvinen, 2013 (1)
1.090 [1.000, 1.188]
RE Model
1.034 [1.007, 1.062]
0
1
2
3
4
5
Coefficient of Variation Ratio

R-Code

Descriptive analysis

```r
# libraries and data ------------------------------------------------------
library(dplyr)
library(haven)
library(ggplot2)
library(ggpubr)

# read data
data <- read_sas("analysedatensatz_20210716.sas7bdat")

# delete trial T70
data <- data[-c(681, 682), ]


# description -------------------------------------------------------------
# number of trials
length(unique(data$StudyID))

# number of individual observations (n_completed)
sum(data$n_completed)

# arms per trial
arms <- data %>%
          group_by(StudyID) %>%
          summarize(number = n()) %>%
          as.data.frame()


# arms with LogMean, LogSD and n_completed
compl <- data %>%
          group_by(StudyID) %>%
          summarize(complete = sum(complete.cases(LogMean, LogSD,
                                                  n_completed))) %>%
          as.data.frame()

# merge
comp <- merge(arms, compl, by = "StudyID")

# number of trials with LogMean, LogSD and n_completed
sum(comp$number == comp$complete)

# number of individual observations (n_completed)
stud <- comp[comp$number == comp$complete, ]
stud <- data[data$StudyID %in% stud$StudyID, ]
sum(stud$n_completed)


# drug classes ------------------------------------------------------------
# number of drug classes
drugclasses <- data %>%
                group_by(Drugclass) %>%
```

```
                summarize(number = n()) %>%
                as.data.frame()

# number of treatment groups
sum(drugclasses$number[1:10])

# convert Drugclass to factor
drugclasses$Drugclass <- as.factor(drugclasses$Drugclass)

# barplot
barplot_drugclasses <- ggplot(drugclasses[1:10, ],
                              aes(x = reorder(Drugclass, -number),
                                  y = number)) +
                        geom_bar(stat = "identity", fill = "#473C8B") +
                        labs(title = "Number of drug classes",
                             y = "Frequency", x = "Drug class") +
                        scale_x_discrete(labels = c("DPP-4-Inhibitors/
                                                     Gliptines",
                                                    "GLP-1-Receptor-Agonists",
                                                    "SGLT-2-Inhibitors",
                                                    "Thiazolidinediones/
                                                     Glitazones",
                                                    "Alpha-Glucosidase-
                                                     Inhibitors",
                                                    "Metformin",
                                                    "Combination",
                                                    "Sulfonylureas",
                                                    "Others",
                                                    "Insulins")) +
                        coord_flip() +
                        theme_bw() +
                        theme(plot.title = element_text(size = 24,
                                                        margin =
                                                          margin(0,0,8,0)),
                              axis.title.x = element_text(size = 22,
                                                          margin =
                                                            margin(0,8,0,0)),
                              axis.title.y = element_text(size = 22,
                                                          margin =
                                                            margin(0,8,0,0)),
                              axis.text.x = element_text(size = 20),
                              axis.text.y = element_text(size = 20),
                              legend.position = "none")
ggsave(path = "graphics", filename = "barplot_drugclasses.png",
       plot = barplot_drugclasses, width = 20, height = 13, units = "in")

# delete title
barplot_drugclasses_without_title <- barplot_drugclasses +
                                     theme(plot.title = element_blank())
ggsave(path = "graphics", filename = "barplot_drugclasses_without_title.png",
       plot = barplot_drugclasses_without_title, width = 20, height = 13,
       units = "in")


```

```r
# convert Placebo to factor ------------------------------------------------
data$Placebo <- as.factor(data$Placebo)


# dataframes with statistical parameters ----------------------------------
# dm_years, men, age, weight, BMI, hba1c_bl
vars <- c("dm_years", "men", "age", "weight", "BMI", "hba1c_bl")
for (i in vars) {
  assign(paste(i, "_df", sep = ""),
         data %>%
         group_by(Placebo) %>%
         summarize(mean = mean(get(i), na.rm = TRUE),
                   median = median(get(i), na.rm = TRUE),
                   first_quartile = quantile(get(i),
                                             probs = 0.25, na.rm = TRUE),
                   third_quartile = quantile(get(i),
                                             probs = 0.75, na.rm = TRUE),
                   minimum = min(get(i), na.rm = TRUE),
                   maximum = max(get(i), na.rm = TRUE)) %>%
         as.data.frame())
}

# hba1c_end (exp(LogMean))
hba1c_end_df <- data %>%
                  group_by(Placebo) %>%
                  summarize(mean = mean(exp(LogMean), na.rm = TRUE),
                            median = median(exp(LogMean), na.rm = TRUE),
                            first_quartile = quantile(exp(LogMean),
                                                      probs = 0.25,
                                                      na.rm = TRUE),
                            third_quartile = quantile(exp(LogMean),
                                                      probs = 0.75,
                                                      na.rm = TRUE),
                            minimum = min(exp(LogMean), na.rm = TRUE),
                            maximum = max(exp(LogMean), na.rm = TRUE)) %>%
                  as.data.frame()

# hba1c_end_SD (exp(LogSD - 1/(2*n_completed)))
sd_df <- data %>%
           group_by(Placebo) %>%
           summarize(mean = mean(exp(LogSD - 1/(2*n_completed)),
                                 na.rm = TRUE)) %>%
           as.data.frame()

# duration
groups <- data[!duplicated(data$StudyID), ]
duration_df <- groups %>%
                  summarize(mean = mean(duration, na.rm = TRUE),
                            median = median(duration, na.rm = TRUE),
                            first_quartile = quantile(duration,
                                                      probs = 0.25,
                                                      na.rm = TRUE),
                            third_quartile = quantile(duration,
                                                      probs = 0.75,
```

```
                                                    na.rm = TRUE),
                          minimum = min(duration, na.rm = TRUE),
                          maximum = max(duration, na.rm = TRUE)) %>%
                as.data.frame()


# boxplots baseline characteristics -------------------------------------
# dm_years
boxplot_dm_years <- ggplot(data, aes(x = Placebo, y = dm_years)) +
                      geom_boxplot(aes(fill = Placebo), na.rm = TRUE) +
                      scale_y_continuous(limits = c(0, 20),
                                         breaks = c(0, 5, 10, 15, 20)) +
                      scale_fill_manual(values = c("#FFA500", "#00868B"),
                                        name = "Group",
                                        breaks = c("0", "1"),
                                        labels = c("experimental",
                                                   "control")) +
                      labs(title = "Boxplot of duration of diabetes per group",
                           y = "Duration of diabetes [years]",
                           x = element_blank()) +
                      theme_bw() +
                      theme(plot.title = element_text(size = 24,
                                                      margin =
                                                        margin(0,0,8,0)),
                            axis.title.x = element_blank(),
                            axis.title.y = element_text(size = 22,
                                                        margin =
                                                          margin(0,8,0,0)),
                            axis.text.x = element_blank(),
                            axis.text.y = element_text(size = 20),
                            legend.key.size = unit(1, "cm"),
                            legend.title = element_text(size = 22),
                            legend.text = element_text(size = 20),
                            axis.ticks.x = element_blank())
ggsave(path = "graphics", filename = "boxplot_dm_years.png",
       plot = boxplot_dm_years, width = 20, height = 13, units = "in")

# men
boxplot_men <- ggplot(data, aes(x = Placebo, y = men)) +
                  geom_boxplot(aes(fill = Placebo), na.rm = TRUE) +
                  scale_y_continuous(limits = c(0, 100),
                                     breaks = c(0, 25, 50, 75, 100)) +
                  scale_fill_manual(values = c("#FFA500", "#00868B"),
                                    name = "Group",
                                    breaks = c("0", "1"),
                                    labels = c("experimental",
                                               "control")) +
                  labs(title = "Boxplot of proportion of men per group",
                       y = "Proportion of men [%]",
                       x = element_blank()) +
                  theme_bw() +
                  theme(plot.title = element_text(size = 24,
                                                  margin =
                                                    margin(0,0,8,0)),
```

```
                        axis.title.x = element_blank(),
                        axis.title.y = element_text(size = 22,
                                                    margin =
                                                      margin(0,8,0,0)),
                        axis.text.x = element_blank(),
                        axis.text.y = element_text(size = 20),
                        legend.key.size = unit(1, "cm"),
                        legend.title = element_text(size = 22),
                        legend.text = element_text(size = 20),
                        axis.ticks.x = element_blank())
ggsave(path = "graphics", filename = "boxplot_men.png",
       plot = boxplot_men, width = 20, height = 13, units = "in")

# age
boxplot_age <- ggplot(data, aes(x = Placebo, y = age)) +
                  geom_boxplot(aes(fill = Placebo), na.rm = TRUE) +
                  scale_y_continuous(limits = c(0, 80),
                                     breaks = c(0, 20, 40, 60, 80)) +
                  scale_fill_manual(values = c("#FFA500", "#00868B"),
                                    name = "Group",
                                    breaks = c("0", "1"),
                                    labels = c("experimental",
                                               "control")) +
                  labs(title = "Boxplot of age per group",
                       y = "Age [years]",
                       x = element_blank()) +
                  theme_bw() +
                  theme(plot.title = element_text(size = 24,
                                                  margin =
                                                    margin(0,0,8,0)),
                        axis.title.x = element_blank(),
                        axis.title.y = element_text(size = 22,
                                                    margin =
                                                      margin(0,8,0,0)),
                        axis.text.x = element_blank(),
                        axis.text.y = element_text(size = 20),
                        legend.key.size = unit(1, "cm"),
                        legend.title = element_text(size = 22),
                        legend.text = element_text(size = 20),
                        axis.ticks.x = element_blank())
ggsave(path = "graphics", filename = "boxplot_age.png",
       plot = boxplot_age, width = 20, height = 13, units = "in")

# weight
boxplot_weight <- ggplot(data, aes(x = Placebo, y = weight)) +
                     geom_boxplot(aes(fill = Placebo), na.rm = TRUE) +
                     scale_y_continuous(limits = c(0, 120),
                                        breaks = c(0, 20, 40, 60,
                                                   80, 100, 120)) +
                     scale_fill_manual(values = c("#FFA500", "#00868B"),
                                       name = "Group",
                                       breaks = c("0", "1"),
                                       labels = c("experimental",
                                                  "control")) +
```

```
                      labs(title = "Boxplot of body weight per group",
                           y = "Body weight [kg]",
                           x = element_blank()) +
                      theme_bw() +
                      theme(plot.title = element_text(size = 24,
                                                      margin =
                                                        margin(0,0,8,0)),
                            axis.title.x = element_blank(),
                            axis.title.y = element_text(size = 22,
                                                        margin =
                                                          margin(0,8,0,0)),
                            axis.text.x = element_blank(),
                            axis.text.y = element_text(size = 20),
                            legend.key.size = unit(1, "cm"),
                            legend.title = element_text(size = 22),
                            legend.text = element_text(size = 20),
                            axis.ticks.x = element_blank())
ggsave(path = "graphics", filename = "boxplot_weight.png",
       plot = boxplot_weight, width = 20, height = 13, units = "in")

# BMI
boxplot_BMI <- ggplot(data, aes(x = Placebo, y = BMI, fill = Placebo)) +
                  geom_boxplot(aes(fill = Placebo), na.rm = TRUE) +
                  scale_y_continuous(limits = c(0, 50),
                                     breaks = c(0, 10, 20, 30, 40, 50)) +
                  scale_fill_manual(values = c("#FFA500", "#00868B"),
                                    name = "Group",
                                    breaks = c("0", "1"),
                                    labels = c("experimental",
                                               "control")) +
                  labs(title = "Boxplot of BMI per group",
                       y = expression("BMI [" ~ kg/m^{2} * "]"),
                       x = element_blank()) +
                  theme_bw() +
                  theme(plot.title = element_text(size = 24,
                                                  margin =
                                                    margin(0,0,8,0)),
                        axis.title.x = element_blank(),
                        axis.title.y = element_text(size = 22,
                                                    margin =
                                                      margin(0,8,0,0)),
                        axis.text.x = element_blank(),
                        axis.text.y = element_text(size = 20),
                        legend.key.size = unit(1, "cm"),
                        legend.title = element_text(size = 22),
                        legend.text = element_text(size = 20),
                        axis.ticks.x = element_blank())
ggsave(path = "graphics", filename = "boxplot_BMI.png",
       plot = boxplot_BMI, width = 20, height = 13, units = "in")

# hba1c_bl
boxplot_hba1c_bl <- ggplot(data, aes(x = Placebo, y = hba1c_bl)) +
                      geom_boxplot(aes(fill = Placebo), na.rm = TRUE) +
                      scale_y_continuous(limits = c(0, 15),
```

```
                                          breaks = c(0, 5, 10, 15)) +
                        scale_fill_manual(values = c("#FFA500", "#00868B"),
                                          name = "Group",
                                          breaks = c("0", "1"),
                                          labels = c("experimental",
                                                     "control")) +
                        labs(title = expression("Boxplot of" ~ HbA[1*c] ~
                                                "at baseline per group"),
                             y = expression(HbA[1*c] ~ "[%] at baseline"),
                             x = element_blank()) +
                        theme_bw() +
                        theme(plot.title = element_text(size = 24,
                                                        margin =
                                                          margin(0,0,8,0)),
                              axis.title.x = element_blank(),
                              axis.title.y = element_text(size = 22,
                                                          margin =
                                                            margin(0,8,0,0)),
                              axis.text.x = element_blank(),
                              axis.text.y = element_text(size = 20),
                              legend.key.size = unit(1, "cm"),
                              legend.title = element_text(size = 22),
                              legend.text = element_text(size = 20),
                              axis.ticks.x = element_blank())
ggsave(path = "graphics", filename = "boxplot_hba1c_bl.png",
       plot = boxplot_hba1c_bl, width = 20, height = 13, units = "in")

# delete title and legend
boxplot_dm_years_without_title <- boxplot_dm_years +
                                    theme(plot.title = element_blank(),
                                          legend.position = "none")
boxplot_men_without_title <- boxplot_men +
                               theme(plot.title = element_blank(),
                                     legend.position = "none")
boxplot_age_without_title <- boxplot_age +
                               theme(plot.title = element_blank(),
                                     legend.position = "none")
boxplot_weight_without_title <- boxplot_weight +
                                  theme(plot.title = element_blank(),
                                        legend.position = "none")
boxplot_BMI_without_title <- boxplot_BMI +
                               theme(plot.title = element_blank(),
                                     legend.position = "none")
boxplot_hba1c_bl_without_title <- boxplot_hba1c_bl +
                                    theme(plot.title = element_blank(),
                                          legend.position = "none")

# arrange
boxplots_characteristics <- ggarrange(boxplot_dm_years_without_title,
                                      boxplot_men_without_title,
                                      boxplot_age_without_title,
                                      boxplot_weight_without_title,
                                      boxplot_BMI_without_title,
                                      boxplot_hba1c_bl_without_title,
```

```
                                      common.legend = TRUE, legend = "bottom")
ggsave(path = "graphics", filename = "boxplots_characteristics.png",
       plot = boxplots_characteristics, width = 20, height = 13, units = "in")


# barplot hhba1c_end (exp(LogMean)) with errorbar -------------------------
errorbar_df <- data %>%
                group_by(Placebo) %>%
                summarize(errorbar1 = mean(exp(LogMean), na.rm = TRUE) -
                            mean(exp(LogSD - 1/(2*n_completed)), na.rm = TRUE),
                          errorbar2 = mean(exp(LogMean), na.rm = TRUE) +
                            mean(exp(LogSD - 1/(2*n_completed)), na.rm = TRUE),
                          mean_LogMean = mean(exp(LogMean), na.rm = TRUE)) %>%
                as.data.frame()

barplot_hba1c_end <- ggplot(errorbar_df, aes(x = Placebo, y = mean_LogMean,
                                             fill = Placebo)) +
                        geom_bar(stat = "identity", width = 0.5) +
                        geom_errorbar(aes(ymin = errorbar1,
                                          ymax = errorbar2),
                                      width = 0.5, size = 1) +
                        scale_x_discrete(breaks = c("0", "1"),
                                         labels = c("experimental",
                                                    "control")) +
                        scale_fill_manual(values = c("#FFA500", "#00868B")) +
                        labs(title = expression("Barplot of mean" ~ HbA[1*c] ~
                                                "after treatment per group"),
                             y = expression(HbA[1*c] ~ "[%] after treatment"),
                             x = "Group") +
                        theme_bw() +
                        theme(plot.title = element_text(size = 24,
                                                        margin =
                                                          margin(0,0,8,0)),
                              axis.title.x = element_text(size = 22,
                                                          margin =
                                                            margin(0,8,0,0)),
                              axis.title.y = element_text(size = 22,
                                                          margin =
                                                            margin(0,8,0,0)),
                              axis.text.x = element_text(size = 20),
                              axis.text.y = element_text(size = 20),
                              legend.position = "none")
ggsave(path = "graphics", filename = "barplot_hba1c_end.png",
       plot = barplot_hba1c_end, width = 20, height = 13, units = "in")

# delete title
barplot_hba1c_end_without_title <- barplot_hba1c_end +
                                    theme(plot.title = element_blank())
ggsave(path = "graphics", filename = "barplot_hba1c_end_without_title.png",
       plot = barplot_hba1c_end_without_title, width = 20, height = 13,
       units = "in")
```

Meta-analysis

```r
# libraries and data ------------------------------------------------------
library(dplyr)
library(haven)
library(metafor)
library(tidyr)

# read data
data <- read_sas("analysedatensatz_20210716.sas7bdat")

# convert to wide format
data_wide <- pivot_wider(data = data,
                         id_cols = c("StudyID", "StudyAbb", "duration"),
                         names_from = "Placebo",
                         values_from = c("LogSD", "Weight_LogSD", "LogSD_ADJ",
                                         "n_completed", "LogMean", "Drug",
                                         "Drugclass", "dm_years", "age", "men",
                                         "hba1c_bl", "weight", "BMI"))

# number of placebo arms per trial
lengths(data_wide$LogMean_1)

# trials with 0 oder more than 1 placebo arm
unname(data_wide[which((lengths(data_wide$LogMean_1) != 1) == TRUE), ]$StudyID)
# -> S213, P1037, P1111, P1163, T70, T51, T429

# split trials with more than 1 placebo arm
for (i in c(231, 232, 364, 365, 366, 476, 477, 564,
            565, 566, 754, 755, 756, 757, 780, 781)) {
        data[i, "StudyID"] <- paste(data[i, "StudyID"], "a", sep = "")
        data[i, "StudyAbb"] <- paste(data[i, "StudyAbb"], "a", sep = "")
}
for (i in c(233, 234, 367, 368, 478, 479, 567,
            568, 758, 759, 760, 761, 782, 783)) {
        data[i, "StudyID"] <- paste(data[i, "StudyID"], "b", sep = "")
        data[i, "StudyAbb"] <- paste(data[i, "StudyAbb"], "b", sep = "")
}
for (i in c(369, 370)) {
        data[i, "StudyID"] <- paste(data[i, "StudyID"], "c", sep = "")
        data[i, "StudyAbb"] <- paste(data[i, "StudyAbb"], "c", sep = "")
}

# rename T-Emerge trials
data[c(105, 106, 107), "StudyAbb"] <- "T-Emerge2012"
data[c(243, 244), "StudyAbb"] <- "T-Emerge2013"

# delete trial T70
data <- data[-c(681, 682), ]

# convert to wide format
data_wide <- pivot_wider(data = data,
                         id_cols = c("StudyID", "StudyAbb", "duration"),
                         names_from = "Placebo",
```

```
                          values_from = c("LogSD", "Weight_LogSD", "LogSD_ADJ",
                                          "n_completed", "LogMean", "Drug",
                                          "Drugclass", "dm_years", "age", "men",
                                          "hba1c_bl", "weight", "BMI"))

# one row for each comparison
unnested_data <- unnest(data_wide,
                        cols = c(LogSD_0, Weight_LogSD_0, LogSD_ADJ_0,
                                 n_completed_0, LogMean_0, Drug_0,
                                 Drugclass_0, dm_years_0, age_0, men_0,
                                 hba1c_bl_0, weight_0, BMI_0))

# unlist each column
unlisted_data <- data.frame(lapply(unnested_data, function(x) unlist(x)))


# meta-analysis ------------------------------------------------------------
# calculate ln CVR
meta_data <- escalc(measure = "CVR",
                    n2i = unlisted_data$n_completed_1,
                    sd2i = exp(unlisted_data$LogSD_1 -
                               1/(2*(unlisted_data$n_completed_1 - 1))),
                    m2i = exp(unlisted_data$LogMean_1),
                    n1i = unlisted_data$n_completed_0,
                    sd1i = exp(unlisted_data$LogSD_0 -
                               1/(2*(unlisted_data$n_completed_0 - 1))),
                    m1i = exp(unlisted_data$LogMean_0),
                    data = unlisted_data)

# number of pairwise eligible comparisons
sum(!is.na(meta_data$yi))

# summary of ln CVR
summary(exp(meta_data$yi))

# id per group for slab argument
meta_data <- meta_data %>%
                group_by(StudyID) %>%
                mutate(id = row_number())

# random effects model
re_model <- rma(yi = yi, vi = vi, weighted = TRUE, method = "DL",
                slab = paste0(
                        unlist(
                        regmatches(x = meta_data$StudyAbb,
                                   m = gregexpr(pattern = "(^[\u00C0-\u017FA-z
                                       -]+_([0-9]){1})|(^[\u00C0-\u017FA-z-]+)",
                                                text = meta_data$StudyAbb,
                                                perl = TRUE))),
                        ", ",
                        unlist(
                        regmatches(x = meta_data$StudyAbb,
                                   m = gregexpr(pattern = "(?≤\\D|_2|_3)[0-9]{4
                                       }[abc]{0,1}$",
```

```
                                                text = meta_data$StudyAbb,
                                                perl = TRUE))),
                        " (",
                        meta_data$id,
                        ")"),
                data = meta_data)

# extract weights of random effects model with inverse variance weights
W <- diag(1/(re_model$vi + re_model$tau2), nrow = re_model$k, ncol = re_model$k)
wi <- as.vector(diag(W))
manual <- rep(NA_real_, re_model$k.f)
manual[re_model$not.na] <- wi
weight_sum <- sum(manual, na.rm = TRUE)

# edit weights.rma.uni in metafor package for splitting plots
metafor <- asNamespace("metafor")
.weights.rma.uni <- get("weights.rma.uni", envir = metafor)
.get.mstyle <- get(".get.mstyle", envir = metafor)
.chkclass <- get(".chkclass", envir = metafor)

my.weights.rma.uni <- function (object, type = "diagonal", ...) {
        mstyle <- .get.mstyle("crayon" %in% .packages())
        .chkclass(class(object), must = "rma.uni", notav = "rma.uni.selmodel")
        na.act <- getOption("na.action")
        if (!is.element(na.act, c("na.omit", "na.exclude",
                                  "na.fail", "na.pass")))
             stop(mstyle$stop("Unknown 'na.action' specified under options()."))
        type <- match.arg(type, c("diagonal", "matrix"))
        x <- object
        if (x$weighted) {
                if (is.null(x$weights)) {
                        W <- diag(1/(x$vi + x$tau2), nrow = x$k, ncol = x$k)
                }
                else {
                        W <- diag(x$weights, nrow = x$k, ncol = x$k)
                }
        }
        else {
                W <- diag(1/x$k, nrow = x$k, ncol = x$k)
        }
        if (type == "diagonal") {
                wi <- as.vector(diag(W))
                weight <- rep(NA_real_, x$k.f)
                weight[x$not.na] <- wi/weight_sum * 100
                names(weight) <- x$slab
                if (na.act == "na.omit")
                        weight <- weight[x$not.na]
                if (na.act == "na.fail" && any(!x$not.na))
                        stop(mstyle$stop("Missing values in weights."))
                return(weight)
        }
        if (type == "matrix") {
                Wfull <- matrix(NA_real_, nrow = x$k.f, ncol = x$k.f)
                Wfull[x$not.na, x$not.na] <- W
```

```
                rownames(Wfull) <- x$slab
                colnames(Wfull) <- x$slab
                if (na.act == "na.omit")
                        Wfull <- Wfull[x$not.na, x$not.na, drop = FALSE]
                if (na.act == "na.fail" && any(!x$not.na))
                        stop(mstyle$stop("Missing values in results."))
                return(Wfull)
        }
}

assignInNamespace("weights.rma.uni", my.weights.rma.uni, metafor)

# rerun rma with manual weights
manual_model <- rma(yi = yi, vi = vi, weighted = TRUE, weights = manual,
                    method = "DL",
                    slab = paste0(
                            unlist(
                            regmatches(x = meta_data$StudyAbb,
                                       m = gregexpr(pattern = "(^[\u00C0-\u017FA
                                           -z-]+_([0-9]){1})|(^[\u00C0-\u017FA-z
                                           -]+)",
                                                    text = meta_data$StudyAbb,
                                                    perl = TRUE))),
                            ", ",
                            unlist(
                            regmatches(x = meta_data$StudyAbb,
                                       m = gregexpr(pattern = "(?≤\\D|_2|_3)[0-9
                                           ]{4}[abc]{0,1}$",
                                                    text = meta_data$StudyAbb,
                                                    perl = TRUE))),
                            " (",
                            meta_data$id,
                            ")"),
                    data = meta_data)

# for-loop to create forest plots
for (i in list(1:20, 21:37, 38:92, 93:118, 119:181, 182:214,
               215:242, 243:262, 263:304, 305:344, 345:372,
               373:395, 396:419, 420:448, 449:477, 478:500)) {
        list_weights <- list(1:17, 18:34, 35:51, 52:68, 69:85, 86:102,
                             103:119, 120:136, 137:153, 154:170, 171:187,
                             188:204, 205:221, 222:238, 239:255, 256:272)
                z <- list(1:20, 21:37, 38:92, 93:118, 119:181, 182:214,
                          215:242, 243:262, 263:304, 305:344, 345:372,
                          373:395, 396:419, 420:448, 449:477, 478:500)
                a <- which(sapply(z, FUN = function(X) i[[1]] %in% X))
                png(filename = paste0("graphics/forestplot", a, ".png"),
                    width = 20, height = 13, units = "in", res = 300)
                forestplot <- manual_model
                forestplot$vi <- forestplot$vi[i]
                forestplot$vi.f <- forestplot$vi.f[i]
                forestplot$yi <- forestplot$yi[i]
                forestplot$yi.f <- forestplot$yi.f[i]
                forestplot$slab <- forestplot$slab[i]
```

```
                forestplot$not.na <- forestplot$not.na[i]
                forestplot$weights <- forestplot$weights[list_weights[[a]]]
                forestplot$k <- 17
                forestplot$k.f <- 17
                forest(forestplot,
                       transf = exp,
                       refline = 1,
                       header = TRUE,
                       digits = 3L,
                       cex = 1.7)
                dev.off()
}

# re-edit weights.rma.uni in metafor package
assignInNamespace("weights.rma.uni", .weights.rma.uni, metafor)


# compare calculations of variance of ln CVR ------------------------------
# functions for ln CVR of Nakagawa
# ln CVR
Calc.lnCVR <- function(CMean, CSD, CN, EMean, ESD, EN){
        ES <- log(ESD) - log(EMean) + 1/(2*(EN-1)) -
                (log(CSD) - log(CMean) + 1/(2*(CN-1)))
        return(ES)
}

# variance of ln CVR
Calc.var.lnCVR <- function(CMean, CSD, CN, EMean, ESD, EN,
                           Equal.E.C.Corr = TRUE) {
        if (Equal.E.C.Corr == TRUE) {
                mvcorr <- cor.test(log(c(CMean, EMean)),
                                   log(c(CSD, ESD)))$estimate
                S2 <- CSD^2/(CN*(CMean^2)) + 1/(2*(CN-1)) -
                        2*mvcorr*sqrt((CSD^2/(CN*(CMean^2)))*(1/(2*(CN-1)))) +
                        ESD^2/(EN*(EMean^2)) + 1/(2*(EN-1)) -
                        2*mvcorr*sqrt((ESD^2/(EN*(EMean^2)))*(1/(2*(EN-1))))
        }
        else {
                Cmvcorr <- cor.test(log(CMean), log(CSD))$estimate
                Emvcorr <- cor.test(log(EMean), log(ESD))$estimate
                S2 <- CSD^2/(CN*(CMean^2)) + 1/(2*(CN-1)) -
                        2*Cmvcorr*sqrt((CSD^2/(CN*(CMean^2)))*(1/(2*(CN-1)))) +
                        ESD^2/(EN*(EMean^2)) + 1/(2*(EN-1)) -
                        2*Emvcorr*sqrt((ESD^2/(EN*(EMean^2)))*(1/(2*(EN-1))))
        }
        return(S2)
}

# version1: escalc
version1 <- meta_data$vi
# version2: function of Nakagawa with equal correlation between mean and SD
version2 <- Calc.var.lnCVR(CMean = exp(meta_data$LogMean_1),
                           CSD = exp(meta_data$LogSD_1 -
                                     1/(2*(unlisted_data$n_completed_1 - 1))),
```

```
                            CN = meta_data$n_completed_1,
                            EMean = exp(meta_data$LogMean_0),
                            ESD = exp(meta_data$LogSD_0 -
                                      1/(2*(unlisted_data$n_completed_0 - 1))),
                            EN = meta_data$n_completed_0,
                            Equal.E.C.Corr = TRUE)
# version3: function of Nakagawa with separate correlation between mean and SD
version3 <- Calc.var.lnCVR(CMean = exp(meta_data$LogMean_1),
                            CSD = exp(meta_data$LogSD_1 -
                                      1/(2*(unlisted_data$n_completed_1 - 1))),
                            CN = meta_data$n_completed_1,
                            EMean = exp(meta_data$LogMean_0),
                            ESD = exp(meta_data$LogSD_0 -
                                      1/(2*(unlisted_data$n_completed_0 - 1))),
                            EN = meta_data$n_completed_0,
                            Equal.E.C.Corr = FALSE)
# comparison
df_versions_varlnCVR <- data.frame(version1, version2, version3)
```

Declaration of Authorship

Hereby, I declare that I have composed the presented paper independently on my own and without any other resources than the ones indicated. All thoughts taken directly or indirectly from external sources are properly denoted as such.

München, October 1, 2021
Place, date

Signature