The association between hypomagnesemia and poor glycaemic control in type 1 diabetes is limited to insulin resistant individuals

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In a cohort of adults with type 1 diabetes, we examined the prevalence of hypomagnesemia and the correlation of serum magnesium levels with metabolic determinants, such as glycaemic control (as HbA1c), inflammatory markers and circulating cytokines. Furthermore, we assessed if a surrogate for insulin resistance is essential for the possible association of serum magnesium with metabolic determinants. Individuals with type 1 diabetes, aged above 18 years, were included and clinical characteristics were obtained from questionnaires and clinical records. In venous blood samples we measured cytokines and adipose-tissue specific secretion proteins. Serum magnesium concentrations were measured and correlated with clinical data and laboratory measurements using univariate and multivariate regression models. Hierarchical multiple regression of serum magnesium with insulin resistance was adjusted for diabetes and potential magnesium confounders. The prevalence of hypomagnesemia (serum magnesium levels < 0.7 mmol/L) was 2.9% in a cohort consisting of 241 individuals with type 1 diabetes. The magnesium concentration in the cohort was not associated with HbA1c ($r = -0.12$, $P$-value = 0.068) nor with any inflammatory marker or adipokine. However, insulin dose (IU/kg), a surrogate measure of resistance in type 1 diabetes, moderated the association of serum magnesium (mmol/L) with HbA1c (mmol/mol) with a $B$ coefficient of $-71.91$ (95% CI: $-119.11; -24.71$), $P$-value = 0.003 and Log10 high-sensitivity C-reactive protein (Log10 mg/L) $-2.09$ (95% CI: $-3.70; -0.48$), $P$-value = 0.011). The association of low serum magnesium levels with glycaemic control (HbA1c) and high-sensitivity C-reactive protein in individuals with type 1 diabetes is limited to subjects using a high insulin dose and suggests that insulin resistance, a type 2 diabetes feature, is a prerequisite for hypomagnesemia.

A blood magnesium (Mg$^{2+}$) concentration below 0.7 mmol/L is prevalent in people with type 2 diabetes in comparison to non-diabetic subjects, with reported percentages ranging from 13.5 to 47.7%1. Hypomagnesemia is associated with poor glycaemic control and progression from pre-diabetes to diabetes2,3, while some Mg$^{2+}$ supplementation studies have shown to improve glycaemic control15. Moreover, maintaining physiological Mg$^{2+}$ levels has been suggested to decrease the risk of developing cardiovascular diseases (CVD) in type 2 diabetes2,4.

Hypomagnesemia has also been reported in studies with type 1 diabetes individuals in the eighties and early nineties9,10. However, these results cannot be extrapolated to the present as treatment of type 1 diabetes has significantly improved over the past decades, resulting in better glycaemic control. Indeed, a recent study demonstrates that the prevalence of hypomagnesemia is only 4.3% in a cohort of type 1 diabetes11. Hence, novel studies studying the prevalence and identifying the factors that contribute to hypomagnesemia are warranted.

Here we assess the prevalence of hypomagnesemia in a cohort of type 1 diabetes adults and investigate whether Mg$^{2+}$ levels are associated with clinical characteristics (sex, age, duration of diabetes, smoking and alcohol use), HbA1c, insulin sensitivity, body mass index (BMI), inflammatory markers and adipokines.

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Subjects and Methods

Subjects. Participants were selected from the outpatient diabetes clinic of the Radboud University Medical Center, the Netherlands. Inclusion criteria were a diagnosis of type 1 diabetes (based on clinical diagnosis) and age above eighteen years. Pregnant women were excluded.

This project is part of the Human Functional Genomics Project (HFGP)\textsuperscript{12}. Ethical approval for the study was obtained from the Institutional Review Board of the Radboud University Medical Center (NL.54214.091.15, 2015–1930 and NL.42561.091.12, 2012–550). Participant inclusion and experiments were conducted according to the principles expressed in the Declaration of Helsinki. All participants gave written informed consent before participation.

Demographic and Laboratory Analysis. Clinical characteristics, including age (years), sex (men/women), BMI (kg/m\textsuperscript{2}), blood pressure (mmHg), smoking status (current, former, never), alcohol use (yes, no), duration of diabetes (years), HbA\textsubscript{1C} (mmol/mol), insulin dose (units insulin per day), total cholesterol (mmol/L), triglycerides (TG) (mmol/L) and high density Lipoprotein (HDL) (mmol/L) were obtained from questionnaires and clinical records. Insulin resistance markers were calculated according to Bîcu et al.\textsuperscript{13}. Venous blood was collected after an overnight fasting period. We measured high-sensitivity C-reactive protein (hs-CRP), IL-18 and IL-18 binding protein (IL-18BP), established inflammatory markers that are often elevated in individuals with diabetes, in the EDTA collected plasma samples (R&D duoset ELISA, MN, USA). Serum samples were measured for Mg\textsuperscript{2+} using a calibrated standardized colorimetric assay with a coefficient of variation of 1.98% (Cobas 8000; Roche Diagnostics, Risch-Rotkreuz, Switzerland).

Statistical Analysis. Data are presented as percentages, mean ± SD or median with interquartile range for skewed variables. Pearson's correlation tests (continuous variables), Point-biserial correlations (dichotomous variables), or one-way ANOVA analysis (> 2 groups) were carried out to determine the correlation or difference between serum Mg\textsuperscript{2+} concentrations with demographic parameters or other laboratory measurements in total cohort and based on insulin treatment in units per kg body weight. Independent-samples t-test was run to assess differences between the mean of the high insulin dose (> 0.70 units per kg body weight, IU/kg)) versus low insulin dose (≤ 0.70 IU/kg).

Multivariate analysis was used to assess if serum Mg\textsuperscript{2+} has multiple interaction factors in the association with HbA\textsubscript{1C}, BMI, hs-CRP and Leptin. The linear relationship between continuous variables was assessed by scatterplot. Multicollinearity was assessed by Pearson correlations (r < 0.9). Hierarchical multiple regression was performed to identify if insulin dose (IU/kg) as continuous variable, significantly moderates the association of serum Mg\textsuperscript{2+} with HbA\textsubscript{1C}, BMI, hs-CRP and Leptin. Skewed dependent variables were Log\textsubscript{10} transformed. Homoscedasticity was assessed by visual inspection of the studentized residuals plotted against the predicted values for high versus low insulin dose (IU/kg) individuals. The interaction model of serum Mg\textsuperscript{2+} (mmol/L) * insulin dose (IU/kg) as a continuous variable was adjusted for possible confounders: model 1 is age (years) and sex (men/women) adjusted, model 2 is adjusted for duration of diabetes (years), estimated glomerular filtration rate (eGFR) (< 60, 60–90, > 90 mL/min/1.73m\textsuperscript{2}), alcohol use (yes, no), smoking (current, former, never), TG (mmol/L), LDL cholesterol (mmol/L), systolic blood pressure (mmHg), statins use (yes, no) and proton pump inhibitor (PPI) use (yes, no). Plots of the association of serum Mg\textsuperscript{2+} with outcome variables, crude and corrected for confounders, are visualized using the PROCESS macro in SPSS\textsuperscript{14}. Missing data (< 13%) were imputed for regression analysis using Predictive Mean Matching combing ten iterations and thirteen imputation sets into one imputation model. All data analyses were performed using SPSS for Windows (v25.0.0.01, IBM). P-values ≤ 0.05 were considered statistically significant.

Results

In total, 241 individuals with type 1 diabetes were included in the cohort. Demographic data and laboratory results are shown in Table 1. The mean serum Mg\textsuperscript{2+} concentration was 0.84 ± 0.10 mmol/L, with 7 people (2.9%) that had hypomagnesemia (serum Mg\textsuperscript{2+} < 0.70 mmol/L). Serum Mg\textsuperscript{2+} concentrations were correlated with duration of diabetes (r = 0.15, P-value = 0.017), serum creatinine (r = 0.14, P-value = 0.032) and eGFR (F(2238) = 3.73, P-value = 0.037). The association of serum Mg\textsuperscript{2+} with HbA\textsubscript{1C} was (r = −0.12, P-value = 0.068). All other variables such as demographic characteristics (sex, age, alcohol use, smoking) and laboratory measurements (cholesterol, inflammatory markers and adipokines) were not associated with serum Mg\textsuperscript{2+}. Since studies in individuals with type 2 diabetes have shown strong negative correlations between serum Mg\textsuperscript{2+} and parameters related to insulin sensitivity\textsuperscript{14,15}, we divided the cohort into quartiles based on insulin dose, (determined by the amount of insulin treatment in units per kg body weight). In the quartile with high insulin dose (> 0.70 IU/kg) but not in other quartiles, a clear, inverse, correlation between Mg\textsuperscript{2+} serum level and HbA\textsubscript{1C}, (r = −0.26, P-value = 0.047) was found. In this quartile, Mg\textsuperscript{2+} serum level also correlated with sex (men) (r = 0.30, P-value = 0.021), and inversely with BMI (r = −0.29, P-value = 0.026), Log\textsubscript{10} hs-CRP (r = −0.39, P-value = 0.003) and Log\textsubscript{10} Leptin (r = −0.37, P-value = 0.004). The correlations of serum Mg\textsuperscript{2+} with HbA\textsubscript{1C}, in subjects with a low insulin dose (≤ 0.70 IU/kg), were (r = −0.07, P-value = 0.362) for, BMI (r = 0.03, P-value = 0.714), Log\textsubscript{10} hs-CRP (r = −0.01, P-value = 0.900) and Log\textsubscript{10} Leptin (r = 0.06, P-value = 0.464).

To validate that the high insulin dose (> 0.70 IU/kg) (n = 61) group is truly insulin resistant we assessed widely used insulin resistance markers: TG / HDL ratio, TG levels and total cholesterol/HDL ratio\textsuperscript{13}. All insulin resistance markers were statistically higher in the group that used > 0.70 IU/kg compared to the low insulin use group, with a difference of 0.64 (95% CI: 0.54; 0.86), t(205) = 6.14, P-value = < 0.001 for TG / HDL ratio, 0.55 (95% CI: 0.33; 0.77), t(205) = 4.97, P-value = < 0.001 for TG and 0.52 (95% CI: 0.24; 0.80), t(2.13) = 3.64, p-value = < 0.001.
To identify if there was an interaction between serum Mg$^{2+}$ with sex and insulin dose on outcome variables HbA$_1c$, BMI, Log$_{10}$ hs-CRP and Log$_{10}$ Leptin we performed a multivariate analysis. The interaction effect between sex and serum Mg$^{2+}$ on the combined dependent variables (HbA$_1c$, BMI, Log$_{10}$ hs-CRP and Log$_{10}$ Leptin) was not statistically significant, F(4, 232) = 0.55, $P$-value = 0.703, partial $\eta^2 = 0.009$. There was a statistically significant interaction effect between insulin dose and serum Mg$^{2+}$ on the combined dependent variables, F(4, 232) = 2.97, $P$-value = 0.024, partial $\eta^2 = 0.059$. The results of the multivariate analysis per individual dependent variable is reported in Supplementary table 1.

As follow-up analysis, hierarchical multiple regression was used to assess the interaction effect of continuous insulin resistance with serum Mg$^{2+}$ and analyzed by multivariable linear regression on the association of outcome variables: HbA$_1c$, BMI, Log$_{10}$ hs-CRP and Log$_{10}$ Leptin. Insulin dose moderated the effect of serum Mg$^{2+}$ on HbA$_1c$ and Log$_{10}$ hs-CRP, as evidenced by a statistically significant increase in total variation explained of 5.0% (F(1, 237) = 13.71, $P$-value = < 0.001) for HbA$_1c$, and 3.5% (F(1, 237) = 8.82, $P$-value = 0.004) for Log$_{10}$ hs-CRP. After adjusting for confounders, the moderator effect of insulin dose and serum Mg$^{2+}$ remained in the association with HbA$_1c$ − 71.91 (95% CI: − 119.11; − 24.71), $P$-value = 0.003 (Table 2) and Log$_{10}$ hs-CRP − 2.09 (95% CI: − 3.70; − 0.48), $P$-value = 0.011 (Table 3). Plotting the interaction shows that insulin dose is critical for the negative association of serum Mg$^{2+}$ with HbA$_1c$ and hs-CRP (Fig. 1). The crude associations between serum Mg$^{2+}$, HbA$_1c$, Log$_{10}$ hs-CRP and insulin dose are visualized in Supplementary Fig. 1. The interaction effect of

| Demographic variables |  |
|-----------------------|--|
| Men (%)               | 54 |
| Age (years)           | 52 ± 16 |
| Duration of diabetes (years) | 28.4 ± 15.7 |
| Alcohol use, n (%)    | 73 |

| Smoking, n (%) |  |
|----------------|--|
| Current        | 11 |
| Former         | 40 |
| Never          | 48 |

| Metabolic variables |  |
|---------------------|--|
| BMI (kg/m$^2$)      | 25.8 ± 4.4 |
| HbA$_1c$ (%)        | 8.0 ± 1.3 |
| HbA$_1c$ (mmol/mol) | 64 ± 15 |
| Daily insulin dose (IU/kg) | 0.57 (0.44–0.70) |
| Albumin Creatine ratio (mg/mmol) | 0.80 (0.50–1.90) |
| Serum creatinine (µmol/L) | 73 (64–78) |
| Total cholesterol (mmol/L) | 4.65 ± 0.88 |
| TG (mmol/L)         | 0.95 (0.72–1.38) |
| LDL (mmol/L)        | 2.65 ± 0.76 |
| HDL (mmol/L)        | 1.67 ± 0.54 |
| Systolic Blood Pressure (mmHg) | 131 ± 17 |
| Diastolic Blood Pressure (mmHg) | 73 ± 10 |
| eGFR (mL/min/1.73m$^2$), n % |  |
| < 60                | 13 |
| 60–90              | 31 |
| > 90               | 56 |

| Cytokines, hormones and inflammatory markers |  |
|---------------------------------------------|--|
| hs-CRP (mg/L)                             | 0.90 (0.36–2.25) |
| IL18-bp/IL18 complex (ng/mL)               | 1.74 (1.30–2.12) |
| Alpha-1 antitrypsin (mg/mL)                | 0.46 (0.36–0.62) |
| Adiponectin (µg/mL)                       | 4.12 (2.79–6.59) |
| Leptin (ng/mL)                             | 7.85 (3.30–16.44) |
| Resistin (pg/mL)                           | 12.66 (10.20–16.10) |

| Medication use, n (%) |  |
|----------------------|--|
| Metformin            | 2 (0.8) |
| PPI                  | 34 (14.1) |
| Statins              | 84 (34.9) |

Table 1. Characteristics of individuals with type 1 diabetes in the DM300 cohort (n = 241). Characteristics are presented as n (%), or mean ± SD, or median (interquartile rang). BMI = Body Mass Index, HDL = high density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, IL18-bp = interleukin 18-binding protein, PPI = proton pump inhibitor, TG = triglycerides.
of serum Mg\(^{2+}\) with glucose levels\(^{10}\), but since then, diabetes care has substantially improved. The proportion of type 2 diabetes adults (13.5–47.7\%) and historic cohorts of insulin-treated outpatients with diabetes\(^{1,10,18}\). Our study thereby confirms the low prevalence of 4.3\% in a type 1 diabetes cohort of 207 patients published earlier this year\(^{11}\). In 1989, McNair et al. reported a high prevalence of hypomagnesemia (38\%) and inverse correlation of serum Mg\(^{2+}\) with glycaemic control (as HbA\(_1c\)) and hs-CRP that seems to be dependent on insulin resistance. The prevalence of hypomagnesemia in type 1 diabetes in the present cohort is significantly lower than in type 2 diabetes adults (13.5–47.7\%) and historic cohorts of insulin-treated outpatients with diabetes\(^{31,32}\). Our study thereby confirms the low prevalence of 4.3\% in a type 1 diabetes cohort of 207 patients published earlier this year\(^{11}\). In 1989, McNair et al. reported a high prevalence of hypomagnesemia (38\%) and inverse correlation of serum Mg\(^{2+}\) with glucose levels\(^{10}\), but since then, diabetes care has substantially improved. The proportion of type 1 diabetes individuals with good glycaemic control (HbA\(_1c\) from < 7.5\%) has risen from 25 to 45\% while the proportion of people with poor glycaemic control decreased from 40 to 16\%\(^{19}\). Indeed, the average HbA\(_1c\) in our cohort (8.0\%) was lower compared to earlier studies\(^{9,20}\), and comparable to the most recent study having an HbA\(_1c\) of 7.6\%\(^{11}\).

Older studies in type 1 diabetes cohorts have reported the negative association of Mg\(^{2+}\) blood levels with fasting glucose or Hba\(_1c\), or obesity markers in a total cohort of people with type 1 diabetes. The study of Dijk et al. did not assess the effect of insulin resistance and also 86\% the data regarding insulin dose was missing\(^{31}\). In our study, we show that serum Mg\(^{2+}\) is negatively associated with Hba\(_1c\), and Log\(_{10}\) hs-CRP in people that are probably insulin resistant. In a cohort with type 1 and 2 diabetes, the likelihood of having high CRP concentration increased with HbA\(_1c\) levels\(^{10}\). The CRP median in our study is comparable to levels measured in previous type 1 diabetes studies and on average still lower than in individuals with type 2 diabetes\(^{23}\). Interestingly, CRP is associated with a higher risk of developing type 2 diabetes\(^{31}\), while Mg\(^{2+}\) reduces type 2 diabetes incidence\(^{19}\). In the general population, low Mg\(^{2+}\) levels are associated with raised CRP concentration\(^{10}\), and oral Mg\(^{2+}\) supplementation reduces serum CRP levels\(^{26}\). Our results suggest that insulin resistance might be an important determinant in the relation of serum Mg\(^{2+}\) with glycaemic control. We did correct for confounders such as TG and SBP, because these are known to be positively correlated with metabolic insulin resistance. Adjusting for TG and SBP as confounders did not attenuate the moderation effect of insulin dose on the association of serum Mg\(^{2+}\) with Hba\(_1c\), or log transformed hs-CRP\(^{29}\). This suggests that there could be other factors than insulin resistance involved that contribute to hypertriglyceridemia and hypertension in people with type 1 diabetes\(^{31,32}\).

### Table 2. Interaction effect of the moderator insulin dose and serum Mg\(^{2+}\) associated with HbA\(_1c\), Hs-CRP

|          | Crude model | Model 1 | Model 2 |
|----------|-------------|---------|---------|
|          | B (95% CI)  | P-value | B (95% CI) | P-value | B (95% CI) | P-value |
| Constant | −1.04 (−2.07; -0.004) | 0.049 | −0.98 (−2.03; 0.06) | 0.066 | −1.10 (−2.34; 0.14) | 0.081 |
| Serum Mg\(^{2+}\) (mmol/L) | 1.07 (−0.14; 2.27) | 0.082 | 0.91 (−0.29; 2.11) | 0.135 | 0.80 (−0.038; 1.98) | 0.182 |
| Insulin dose (IU/kg) | 2.25 (0.83; 3.67) | 0.002 | 2.01 (0.58; 3.44) | 0.006 | 1.88 (0.49; 3.27) | 0.008 |
| Serum Mg\(^{2+}\) (mmol/L) * insulin dose (IU/kg) | −2.47 (−4.13; 0.82) | 0.003 | −2.17 (−3.83; -0.52) | 0.010 | −2.09 (−3.70; −0.48) | 0.011 |

### Table 3. Interaction effect of the moderator insulin dose and serum Mg\(^{2+}\) associated with Log\(_{10}\) hs-CRP

|          | Crude model | Model 1 | Model 2 |
|----------|-------------|---------|---------|
|          | B (95% CI)  | P-value | B (95% CI) | P-value | B (95% CI) | P-value |
| Constant | −1.04 (−2.07; -0.004) | 0.049 | −0.98 (−2.03; 0.06) | 0.066 | −1.10 (−2.34; 0.14) | 0.081 |
| Serum Mg\(^{2+}\) (mmol/L) | 1.07 (−0.14; 2.27) | 0.082 | 0.91 (−0.29; 2.11) | 0.135 | 0.80 (−0.038; 1.98) | 0.182 |
| Insulin dose (IU/kg) | 2.25 (0.83; 3.67) | 0.002 | 2.01 (0.58; 3.44) | 0.006 | 1.88 (0.49; 3.27) | 0.008 |
| Serum Mg\(^{2+}\) (mmol/L) * insulin dose (IU/kg) | −2.47 (−4.13; 0.82) | 0.003 | −2.17 (−3.83; -0.52) | 0.010 | −2.09 (−3.70; −0.48) | 0.011 |

**Discussion**

This study shows that the prevalence of hypomagnesemia (Mg\(^{2+}\) blood levels < 0.7 mmol/L) in a contemporary cohort of type 1 diabetes adults is only 2.9\%, which is comparable to the normal population\(^{11}\). We also demonstrate an inverse correlation of serum Mg\(^{2+}\) with glycaemic control (as HbA\(_1c\)) and hs-CRP that seems to be dependent on insulin resistance.

The prevalence of hypomagnesemia in type 1 diabetes in the present cohort is significantly lower than in type 2 diabetes adults (13.5–47.7\%) and historic cohorts of insulin-treated outpatients with diabetes\(^{31,32}\). Our study thereby confirms the low prevalence of 4.3\% in a type 1 diabetes cohort of 207 patients published earlier this year\(^{11}\). In 1989, McNair et al. reported a high prevalence of hypomagnesemia (38\%) and inverse correlation of serum Mg\(^{2+}\) with glucose levels\(^{10}\), but since then, diabetes care has substantially improved. The proportion of type 1 diabetes individuals with good glycaemic control (HbA\(_1c\) from < 7.5\%) has risen from 25 to 45\% while the proportion of people with poor glycaemic control decreased from 40 to 16\%\(^{19}\). Indeed, the average HbA\(_1c\) in our cohort (8.0\%) was lower compared to earlier studies\(^{9,20}\), and comparable to the most recent study having a baseline HbA\(_1c\) of 7.6\%\(^{11}\).
The results do explain the high prevalence of hypomagnesemia in type 2 diabetes with insulin resistance being the hallmark of this disorder. Insulin resistance is often associated with being overweight or obese, a factor that is becoming more common in type 1 diabetes too, resulting in the development of “double diabetes”33. The inflammatory marker CRP is even considered as a predictor for pre-diabetes, diabetes and fatty liver disease34–36. This suggests that a similar mechanism of hypomagnesaemia might occur in pathologies that are closely-related to the type 2 diabetes phenotype, such as pre-diabetes and fatty liver disease.

The strengths of this study includes the fact that we studied a large cohort over a wide age range, while other type 1 diabetes studies have determined the incidence in rather small sample sizes of children and adolescents18,37. Another advantage is that we have determined adipose tissue specific lipids and inflammatory cytokines. A limitation is the cross-sectional design study, although we do provide some insight in the mechanism of Mg2+ by using an explanatory statistical model.

In summary, this study shows that serum Mg2+ levels are negatively associated with glycaemic control and inflammation (log10 hs-CRP), but this relationship is limited to people with type 1 diabetes who are probably insulin resistant. These results suggest that hypomagnesemia is not caused by diabetes per se, but that insulin resistance is the main determinant in the association of Mg2+ and glycaemic control in individuals with type 1 and type 2 diabetes.

Data availability
Existing ethical permits do not allow that personal data from this study are deposited in the public domain. The full dataset is available for researchers who meet the criteria for confidential data access as stipulated by participant informed consent and the Institutional Review Board of the Radboud University Medical Center (NL54214.091.15, 2015–1930 and NL42561.091.12, 2012–550).

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Figure 1. Plots of the association of serum Mg2+ with HbA1c and hs-CRP categorized by insulin dose. (A, C) Crude models and (B, D) Model 2, adjusted for: age, sex adjusted, duration of diabetes (years), eGFR (<60, 60–90, >90 mL/min/1.73m2), alcohol use (yes/no), smoking (current, former, never), SBP (mmHg), TG (mmol/L), LDL cholesterol (mmol/L), statins (yes/no) and PPI (yes/no) drugs. eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, hs-CRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, Mg2+ = magnesium, PPI = proton pump inhibitor, SBP = systolic blood pressure, TG = triglycerides.
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Author contributions
L.J.O performed the statistical analysis. L.J.O, J.I.P.v.H., C.J.T. and J.H.F.d.B contributed to the study design. L.J.O, C.J.T. and J.H.F.d.B wrote the manuscript. J.I.P.v.H. and C.J.T. contributed to cohort data collection. C.J.T. and J.H.F.d.B supervised the study. All authors reviewed and approved the final version of the manuscript. J.H.F.d.B. is the guarantor of this work and had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests
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