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Kidney hemodynamic profile and systemic vascular function in adults with type 2 diabetes: Analysis of three clinical trials

Anne C. Hesp [a,*], Mark M. Smits [a], Erik J.M. van Bommel [a], Marcel H.A. Muskiet [a], Lennart Tonneijck [a], Max Nieuwdorp [a], Mark H.H. Kramer [a], Jaap A. Joles [b], Petter Bjornstad [c], Daniël H. van Raalte [a]

[a] Department of Internal Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands
[b] Department of Nephrology & Hypertension, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Department of Pediatrics-Endocrinology, University of Colorado School of Medicine, Aurora, CO, USA

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ABSTRACT

Aims: Glomerular hyperfiltration plays a key role in the pathophysiology of diabetic kidney disease (DKD). Mechanisms underlying this adverse hemodynamic profile are incompletely understood. We hypothesized that systemic vascular pathology, including endothelial dysfunction and arterial stiffness, relates to glomerular hyperfiltration indicated by filtration fraction (FF).

Methods: Baseline data of three trials of overweight adults with type 2 diabetes (TD2, $n = 111$) with relatively well preserved kidney function were analyzed. Glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and FF, were assessed with gold-standard clearance techniques. Systemic vascular resistance (SVR), an indicator of endothelial dysfunction, and pulse pressure (PP), a measure of arterial stiffness, were derived from continuous beat-to-beat monitoring.

Results: SVR related negatively to GFR (β: −0.382, $p < 0.001$) and ERPF (β: −0.475, $p < 0.001$), and positively to FF (β:0.369, $p < 0.001$). Associations between SVR, ERPF and FF persisted after multivariable adjustments.. PP was negatively related to ERPF (β: −0.252, $p = 0.008$), and positively to FF (β: 0.257, $p = 0.006$), of which the latter remained significant in multivariable regression.

Conclusion: Parameters of systemic vascular pathology, including endothelial dysfunction and arterial stiffness, relate to an adverse kidney hemodynamic profile characterized by glomerular hyperfiltration, which predisposes to the development of DKD.

1. Introduction

Diabetic kidney disease (DKD), a common and morbid complication of type 2 diabetes (T2D) affecting up to 40% of patients,[1] is a major driver of cardiovascular disease and the leading cause of end-stage kidney disease.[2] A pathological increase in glomerular filtration rate (GFR), termed hyperfiltration, has been observed early in the course of T2D and is indicated to play a key role in the development of DKD.[3] Conventionally, hyperfiltration is defined as an elevated whole-kidney GFR, i.e. the number of nephrons multiplied by single-nephron GFR, of arbitrarily >130–140 mL/min per 1.73 m^2. However, individuals with a lower number of nephrons may experience single-nephron hyperfiltration while whole-kidney GFR is normal or even in the lower range. In the latter population, filtration fraction (FF), consisting of the GFR relative to the effective renal plasma flow (ERPF), has been proposed to be a better indicator of hyperfiltration.[4]

The underlying mechanisms that induce or sustain this adverse kidney hemodynamic profile have not yet been fully elucidated. However, systemic vascular pathology, as is often observed in adults with diabetes, could have a direct relation and adverse relation with

* Corresponding author at: Diabetes Center, Department of Internal Medicine, Amsterdam University Medical Centers, location VUMC, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands.

E-mail addresses: a.c.hesp@amsterdamumc.nl (A.C. Hesp), mm.smits1@amsterdamumc.nl (M.M. Smits), e.vanbommel@amsterdamumc.nl (E.J.M. van Bommel), ma.muskiet@amsterdamumc.nl (M.H.A. Muskiet), l.tonneijck@amsterdamumc.nl (L. Tonneijck), m.nieuwdorp@amsterdamumc.nl (M. Nieuwdorp), m.kramer@amsterdamumc.nl (M.H.H. Kramer), J.A.Joles@umcutrecht.nl (J.A. Joles), Petter.Bjornstad@childrenscolorado.org (P. Bjornstad), d.vanraalte@amsterdamumc.nl (D.H. van Raalte).

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intrarenal hemodynamics.[5] Previous studies have related large artery stiffness[6–9] and associated pulse pressure (PP),[10] as well as endothelial dysfunction,[11] to adverse kidney outcomes in people with T2D and chronic kidney disease (CKD). Also an increased systemic vascular resistance (SVR), a possible resultant of increased arteriolar vasoconstriction due to endothelial dysfunction, has been shown in CKD with etiologies other than diabetes.[12] However, not all studies support these associations[7,13,14] and importantly, kidney function has almost exclusively been estimated instead of measured in all former studies. In addition, a detailed intrarenal hemodynamic profile in relation to systemic hemodynamics has not yet been constructed.

To address the substantive knowledge gap in the interplay between systemic and kidney hemodynamic function in adults with T2D, we studied markers of vascular function i.e. SVR and PP, in relation to gold-standard measures of kidney hemodynamic profile, including GFR and ERPF and its quotient FF, by inulin and para-aminohippurate (PAH) clearance. We hypothesized that SVR and PP relate to glomerular hyperfiltration as indicated by FF.

2. Subjects, materials and methods

2.1. Research design

We cross-sectionally analyzed the baseline data of adults with T2D of three randomized trials (NCT01744236, NCT02106104, NCT02682563) that were designed to study kidney hemodynamic function before and after treatment with incretin-based therapies or a sodium glucose cotransporter 2 (SGLT2) inhibitor.[15–17] All studies were performed at the clinical trial unit at Amsterdam University Medical Centers, location VUmc. The study protocols were reviewed and approved by local authorities and the ethics review board of the Amsterdam University Medical Centers, location VUmc. The studies complied with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Study population

Participants were recruited from our research database and by advertisements in local newspapers. An oversight of the in- and exclusion criteria of the studies is provided in Appendix A Supplemental 1. In short, eligible participants were men and postmenopausal women, aged 35–75 years, with a body mass index (BMI) $\geq$25 kg/m^2, diagnosed with T2D with an HbA1c of 6.5–9.0% (48–75 mmol/mol). Participants were allowed to use a stable dose ($\geq$3 months) of metformin and/or sulfonylurea for the treatment of T2D, as well as a stable dose ($\geq$3 months) of angiotensin converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARBs) in case of hypertension or albuminuria. Exclusion criteria included an eGFR of <60 mL/min/1.73 m^2, current or recurrent urinary tract infections or active nephritis, urinary retention (determined by bladder ultrasonography after urination at the screening visit), and the use of glucocorticoids, nonsteroidal anti-inflammatory drugs, or diuretics.

2.3. Study protocols, measurements and calculations

Kidney hemodynamics were examined by gold-standard clearance methods using inulin and PAH clearances to measure GFR and ERPF respectively, as described.[16,19] In order to minimize variance of kidney physiology, participants adhered to a 'normal'-salt (9–12 g or 150–200 mmol per day) and -protein (1.5–2 g/kg per day) diet during two days prior to the examinations. In addition, the participants abstained from heavy exercise and alcohol (24 h) as well as caffeine and nicotine (12h) prior to the visit.

After an overnight fast blood and urine were obtained for fasting outcome variables. Kidney hemodynamic assessment then commenced with a weight calculated priming dose of 22.5 mg/kg inulin and 3 mg/kg PAH which was infused in 10 min, followed by a continuous infusion of inulin 11.25 mg/min and PAH 5.33 mg/min for the remainder of the day. Blood was drawn after an equilibration period of 90 min of continuous infusion in order to calculate the kidney hemodynamics based on the plasma clearances. Calculations for measured GFR, ERPF, and FF have previously been described.[16,19] Importantly, FF was calculated by dividing measured GFR by ERPF.

Systemic hemodynamics including SVR and additional variables i.e. blood pressure (RR), heart rate (HR), stroke volume (SV), and cardiac output (CO), were measured in a semi-supine position by continuous beat-to-beat hemodynamic monitoring (Nexfin®, BM Eye, Amsterdam, The Netherlands).[20] This technique obtains a pulse waveform through finger plethysmographic measurements over a period of 30-s, from which it derives SVR, RR, HR, SV, and CO. Pulse pressure was calculated by subtraction of diastolic RR from the systolic RR. Average systemic hemodynamic values were derived using dedicated software (Nexfin@PC version 2, BM Eye, Amsterdam, The Netherlands).

2.4. Statistical analyses

The data are expressed as mean $\pm$ standard deviation (SD) in case of a Gaussian distribution, or median [interquartile range (IQR)] in case of a non-normal distribution. Categorical variables are shown as number (*n*) and expressed in percentages (%). Systemic and kidney hemodynamic data were analyzed by linear regressions; β is shown in the tables. For the assessment of the relation between SVR and kidney hemodynamic variables, crude analyses were performed followed by multivariable linear regressions that corrected for age, sex, body surface area (BSA), and blood glucose at the time of kidney hemodynamic assessment.

In addition, in order to further elucidate the interplay between SVR and kidney hemodynamics, participants were stratified into tertiles of low- medium- and high- SVR. Kidney hemodynamic profile was then examined across tertiles by one-way ANOVA. In case of a significant difference between the tertiles according to the ANOVA, the individual tertiles were compared with the Bonferroni post hoc test.

For the assessment of the relation between PP and kidney hemodynamic variables, crude analyses were performed followed by a multivariable linear regression model that corrects for age, sex, body surface area (BSA), and blood glucose at the time of kidney hemodynamic assessment.

Additional systemic hemodynamic variables including HR, SV, and CO, were examined in relation to kidney hemodynamic variables likewise to the crude and multivariable analyses of SVR and PP.

Lastly, sensitivity analyses were performed in order to test the robustness of the relations between the systemic and kidney hemodynamic variables. To that extent we added HR and SV to the multivariable regressions of PP and kidney hemodynamics, and the use of RAS inhibition to the multivariable regressions of both SVR and PP and kidney hemodynamic variables. Statistical analyses were performed using SPSS software version 26 (IBM Corp, Armonk, NY).

3. Results

3.1. Participant characteristics

Baseline demographic and clinical characteristics are shown in Table 1. A total of

118 participants entered the studies after screening between April 2013 and September 2018. The data of 111 participants were analyzed, due to failure to obtain the results on SVR for seven of the participants. On average, participants were male and overweight, with well-controlled T2D, normal blood pressure, relatively well-preserved kidney function, and minimal albuminuria for a low frequency of patients.

Table 1
Participant characteristics.

Clinical characteristics study (n = 111)	
Age, years	62.9 [58.0–68.0]
Male, *n* (%)	88 (79.3)
Current smoker, *n* (%)	17 (15.3)
BMI, kg/m^2	31.0 [28.2–34.0]
Fasting plasma glucose, mmol/mol	8.1 [7.4–9.2]
HbA1c, mmol/L	56.0 [52.0–60.0]
HbA1c, %	7.3 [6.9–7.6]
Diabetes duration, years	6 [4–12]
Presence of CVD, *n* (%)	18 (15.1)
UACR, mg/mmol	0.86 [0.46–1.96]
Microalbuminuria, *n* (%)	20 (17)
Systemic hemodynamic function parameters	
SBP, mmHg	136.5 (20.5)
DBP, mmHg	68.6 (8.1)
MAP, mmHg	93.9 (11.9)
Pulse pressure, mmHg	67.9 (15.5)
Heart rate, bmp	64 [58–71]
Stroke volume, mL	101.1 (16.5)
Cardiac output, L/min	6.5 (1.2)
Systemic vascular resistance, dyn·s/cm^5	1118 [1017–1300]
Renal hemodynamic function parameters	
GFR, mL/min	107.9 (18.1)
ERPF, mL/min	608.6 (134.7)
FF, %	18 (2)
Use of Medication	
Metformin, n (%)	115 (97.5)
Metformin dose, mg	1700 [1000−2000]
Sulfonylurea, n (%)	25 (22.5)
Antihypertensive, n (%)	69 (62.2)
ACEi, *n* (%)	35 (31.5)
ARB, *n* (%)	31 (27.9)
CA, *n* (%)	22 (19.8)
Beta blocker, *n* (%)	22 (19.8)
Statin, *n* (%)	75 (67.6)
Antiplatelet, *n* (%)	18 (15.1)

Values are expressed as mean (SD) in case of a Gaussian distribution, non-normal data as median [IQR], or -*n* (%). BMI indicated Body Mass Index; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; UACR, urine albumin-to-creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CA, calcium antagonist.

3.2. Associations between systemic vascular resistance and kidney hemodynamics

Univariate regression analyses (Table 2) showed that SVR related negatively to GFR and ERPF (Fig. 1A and B), and related positively to FF (Fig. 1C). After correction for age, sex, BSA, and blood glucose, SVR remained significantly related to ERPF and FF, while the relation with GFR was attenuated (Table 2).

Following the stratification of participants based on low/medium/high SVR, significant differences were observed among tertiles in both systemic and kidney hemodynamic function parameters (Appendix A Supplemental 2) . Notably, participants of the different SVR- tertiles differed significantly in GFR (Fig. 1D), ERPF (Fig. 1E), and FF (Fig. 1F), with decreased GFR and ERPF and increased FF for the higher SVR tertiles. Diabetes control, diabetes duration, and medical management did not differ between groups.

Next, we examined the relation between PP and kidney hemodynamic function and observed a negative relation between PP and ERPF and a positive relation between PP and FF (Table 2). After the correction for age, sex, BSA, blood glucose at the time of kidney hemodynamic

Table 2
Linear regression between systemic vascular parameters SVR and PP and renal hemodynamics.

SVR	Crude model			Model adjusted for age, sex, BSA, and blood glucose		
	β	R^2	p	β	R^2	P
GFR	−0.382	0.146	**<0.001**	−0.086	0.312	0.401
ERPF	−0.475	0.225	**<0.001**	−0.190	0.402	**0.048**
FF	0.369	0.136	**<0.001**	0.232	0.259	**0.030**

PP	Crude model			Model adjusted for age, sex, BSA, and blood glucose, HR, and SV		
	β	R^2	p	β	R^2	P
GFR	−0.126	0.016	0.188	−0.103	0.315	0.401
ERPF	−0.252	0.064	**0.008**	−0.059	0.382	0.481
FF	0.257	0.066	**0.006**	0.199	0.256	**0.049**

Significant differences indicated in boldface type. BSA, body surface area; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; HR, heart rate; PP, pulse pressure; SV, stroke volume; SVR, systemic vascular resistance.

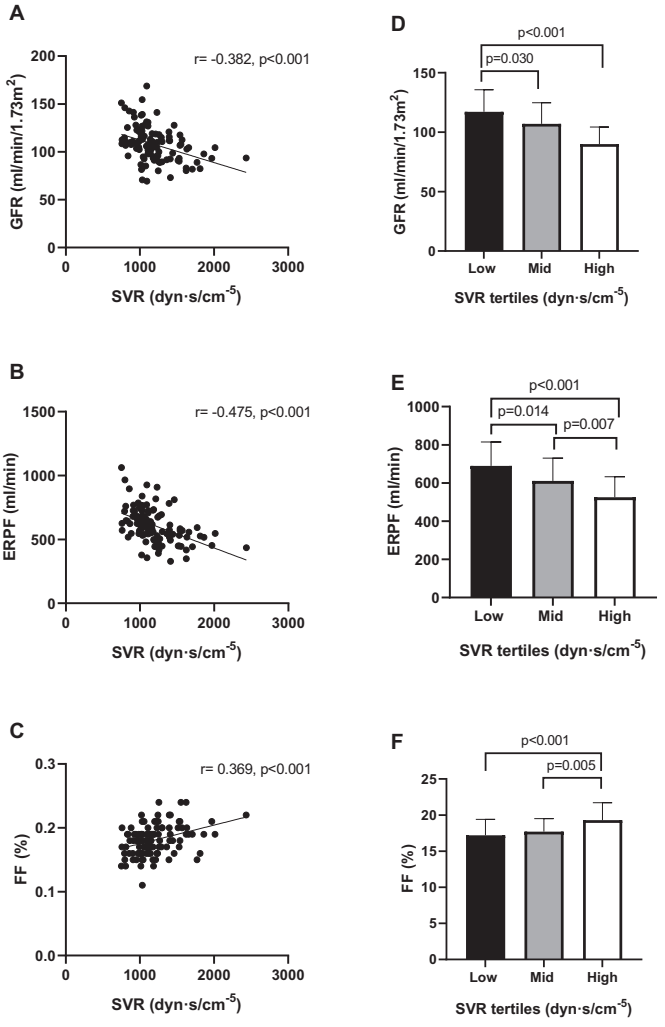

Fig. 1. -A. Association between SVR and GFR. -B. Association between SVR and ERPF. -C. Association between SVR and FF. -D. Glomerular filtration rate (GFR) across systemic vascular resistance (SVR) tertiles. -E. Effective renal plasma flow (ERPF) across SVR tertiles.-F. Filtration fraction (FF) across SVR tertiles. The histograms show the mean ± standard deviation.

assessment, HR, and SV, the relation between PP and FF remained significant.

Conversely, the systemic hemodynamic variables HR, SV, and CO, did not display robust relations to kidney hemodynamic parameters to the same extent (Supplemental 3). Importantly, after correction, HR, SV, and CO did not relate significantly to FF.

Last, sensitivity analyses revealed the addition of HR and SV was of no effect on the relation between PP and kidney hemodynamics. The addition of RAS-use also did not affect the relation between either SVR or PP with kidney hemodynamic variables.

4. Discussion

The current study demonstrates that SVR and PP, as markers of vascular function, relate positively to FF, a marker for single-nephron filtration rate. In addition, SVR showed a negative relation with whole kidney GFR in univariate analyses and with ERPF in multivariate analyses. None of the other measured systemic hemodynamic variables, including HR, SV, and CO demonstrated the same robust associations to FF, which highlights the specific relation of the indices of endothelial dysfunction and arterial stiffness with the intraglomerular hemodynamic profile.

The supraphysiologic increase in GFR, termed hyperfiltration, is a common and early phenomenon in T2D. Importantly, it precedes the development of albuminuria and kidney function decline and is indicated to predispose to DKD.[3] Indeed, a prospective cohort study including 600 individuals with T2D showed that individuals with glomerular hyperfiltration at baseline exhibited a faster decline in measured GFR and progression from microalbuminuria to macroalbuminuria compared to non-hyperfiltering individuals.[21] In addition, although metabolic- and blood pressure control were optimized for all these individuals, hyperfiltration and subsequent GFR decline persisted for a substantial proportion of the participants. This indicates that factors beyond glucose level and blood pressure likely contribute to hyperfiltration, hypothesized to be systemic vascular pathology.

In order to understand the importance of vascular function it is necessary to consider the complexities of kidney physiology. Fundamentally, the kidney is challenged with balancing perfusion and pressure, in order to perform its primary function of glomerular filtration without exposing its capillary network to barotrauma. The pulsatile blood flow following cardiac ejection is tempered first by rapid extension of the large elastic arteries, termed the Windkessel effect, and following by renal autoregulatory mechanisms. In a state of health these autoregulatory mechanisms, i.e. the fast myogenic response and the slow tubuloglomerulofeedback (TGF) system, meticulously regulate blood flow and pressure across a defined range of blood pressure by alteration of the muscle tone and vascular diameter of the kidney arterioles. However, hyperglycemia and insulin resistance are among the key players in the development of vascular damage, including the development of endothelial dysfunction[22] which is characterized by decreased NO-availability and impaired vasodilation, and arterial stiffness.[23] These vascular pathologies can interfere with adequate renal arteriolar caliber modification and can increase incoming pressure oscillations beyond the window of control, which could therefore contribute to kidney damage in the long term.[24]

First, former research has indicated endothelial dysfunction to be present already in prediabetic conditions and early stages of kidney function impairment,[25] and to be associated with long-term kidney function decline.[26] Moreover, the degree of endothelial dysfunction has been associated with the severity of kidney injury (i.e. incipient versus overt nephropathy)[27] and to precede and predict the development of albuminuria,[11,28] which could potentially suggest a causative role. Current research studied SVR as an indicator of endothelial function and its relation to measured kidney hemodynamics in order to elucidate a hemodynamic interaction that could contribute to these adverse kidney outcomes. Importantly, we observed that high SVR relates to a high FF and low ERPF. It could therefore be hypothesized that arteriolar vasoconstriction as a result of endothelial dysfunction decreases kidney perfusion while increasing glomerular pressure and filtration, leading to kidney damage as a result of excessive single nephron workload or barotrauma in the long term.

Second, a body of research has linked arterial stiffness to reduced eGFR in adults with T2D.[6–8] A prospective study even demonstrated arterial stiffness to be an independent predictor of eGFR decline in adults with T2D younger than 60 years of age.[9] The current study, focusing on mechanisms rather than outcome, demonstrated that PP, a common marker for extent of arterial stiffness, related positively to FF. These results suggest that arterial stiffness is associated to an increased vascular pressure at the level of the glomerulus, which could contribute to the observed associations between arterial stiffness and renal function decline.

To our knowledge the current study is the first to make use of the gold-standard clearance techniques with inulin and PAH for the determination of GFR, ERPF, and FF, in relation to systemic vascular measurements. The measurements have been performed in a large and well-phenotyped group of individuals, which provided a strong basis to advance our understanding of the interplay between systemic vascular function and kidney hemodynamic profile, while taking into account potential confounding. Our results indicate that systemic vascular pathology may have a reciprocal effect on kidney function, even before the onset of kidney disease. That knowledge leads to hypothesize that DKD might be prevented by early treatment of systemic vascular damage. Important therapeutics in this regard are those targeting the renin-angiotensin-aldosterone system,[29–33] which have been shown to improve endothelial function and reduce arterial stiffening independent of blood pressure lowering, as well as the recently introduced SGLT2 inhibitors, which have also demonstrated to improve endothelial function and arterial stiffness, as well as reduce renal resistance as determined by ultrasound,[34] and have shown beneficial effects on renal outcomes in several large outcome trials.[35–38]

Our study also has some limitation worth mentioning. First, due to the cross-sectional nature of the study, the causality of the relations cannot be attested. Also, although our measurements of kidney hemodynamics were performed following the gold standard, for systemic vascular measurements surrogate parameters were selected. For future research the determination of systemic vascular measurements by pulse wave velocity, flow-mediated vasodilatation, or even invasive technology, would further contribute to our knowledge of the here-described interactions between systemic vascular function and kidney hemodynamics. In addition, due to the effect of the phase of the menstrual cycle on systemic hemodynamics and kidney hemodynamics we solely included men and post-menopausal women, which poses a restriction on the generalizability of current research. Lastly, although showing clear significance, the explained variance by PP and SVR in the crude models for FF was 13.6% and 6.6% respectively. This underlines the presence of a multifactorial process which could additionally include hyperglycemia and distorted insulin levels, an imbalance in vasoactive humoral mediators, and tubular hyperplasia and hypertrophy.

In conclusion, we demonstrate a positive relation between SVR and PP, as markers of endothelial dysfunction and arterial stiffness, and FF, indicative for single-nephron filtration rate, measured by gold-standard clearance methods in adults with T2D and preserved kidney function. Our study therefore indicates a direct relation between systemic vascular function and kidney hemodynamic profile, which is a promising lead for future research and therapeutic strategies aimed to prevent or treat DKD.

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CRediT authorship contribution statement

A.C. Hesp: Formal analysis, Visualization, Writing- original draft.
M.M. Smits: Investigation, resources, Writing – Review & Editing.
E.J. van Bommel: Investigation, Writing – Review & Editing.
M.H.A. Muskiet: Investigation, Writing – Review & Editing.
L. Tonneijck: Investigation, Writing – Review & Editing.
M. Nieuwdorp: Writing – Review & Editing.
M.H.H. Kramer: Writing – Review & Editing.
J.A. Joles: Writing – Review & Editing.
P. Bjornstad: Supervision, Writing – Review & Editing.
D.H. van Raalte: Supervision, Conceptualisation, Methodology, Funding acquisition, Writing – Review & Editing.

Declaration of competing interest

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Appendix A. Supplementary data

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