High-Normal Thyroid Function and Risk of Atrial Fibrillation

The Rotterdam Study

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Background: Overt and subclinical hyperthyroidism are both well-known independent risk factors for atrial fibrillation. We aimed to investigate the association of high-normal thyroid function with the development of atrial fibrillation in a prospective population-based study in the elderly.

Methods: The association between thyroid-stimulating hormone (TSH) levels and atrial fibrillation was examined in 1426 subjects with TSH levels in the normal range (0.4-4.0 mU/L) and without atrial fibrillation at baseline. In 1177 of the 1426 persons in this group, we also examined the association between free thyroxine levels within the normal range (0.86-1.94 ng/dL [to convert to picomoles per liter, multiply by 12.871]) and atrial fibrillation. During a median follow-up of 8 years, 105 new cases of atrial fibrillation were identified. Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) using Cox proportional hazards models after adjustment for age, sex, current smoking, former smoking, body mass index, systolic blood pressure, hypertension, history of myocardial infarction, presence of heart failure, left ventricular hypertrophy on the electrocardiogram, diabetes mellitus, total cholesterol level, and time of the drawing of blood samples.

Results: The risk of atrial fibrillation was associated with the TSH level. The multivariate adjusted HR was 1.94 (95% CI, 1.13-3.34, lowest vs highest quartile; P for trend, .02). The multivariate adjusted level of free thyroxine showed a graded association with risk of atrial fibrillation (HR, 1.62; 95% CI, 0.84-3.14, highest vs lowest quartile; P for trend, .06).

Conclusion: Within the normal range of thyroid parameters, persons with high-normal thyroid function are at an increased risk of atrial fibrillation.

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Atrial fibrillation is the most common cardiac arrhythmia in the elderly. The prevalence and incidence increase with advancing age.1,2 The disease is associated with a higher risk of stroke,3 peripheral embolism,4 and mortality.5 The treatment of atrial fibrillation is not without danger, as is illustrated by the increased risk of major bleeding and proarrhythmia.6,7 Therefore, prevention of atrial fibrillation is highly preferable, indicating the need of knowledge of the risk factors of atrial fibrillation. Overt hyperthyroidism is a well-known risk factor for atrial fibrillation,8,9 but subclinical hyperthyroidism, defined as a serum thyroid-stimulating hormone (TSH) level below the normal range, with free thyroxine (FT₄) levels within the normal range, has also been identified as a predictor of atrial fibrillation.10-14 Recently, a cross-sectional population-based study showed that the serum FT₄ concentration is independently associated with atrial fibrillation in euthyroid persons with serum TSH levels in the normal range.14 We prospectively investigated the role of parameters of thyroid function in the development of atrial fibrillation in euthyroid persons. The study is part of the population-based Rotterdam Study.

Methods

STUDY POPULATION

The Rotterdam Study is a prospective population-based cohort study that is aimed at assessing the occurrence and progression of and risk factors for chronic diseases in the elderly. Neurogeriatric, cardiovascular, locomotor, and ophthalmologic diseases are the main areas of interest.15 All residents of the Rotterdam suburb of Ommoord, the Netherlands, aged 55
years and older were invited to participate. Of the 10,275 eligible individuals, 7,983 (78%) responded. Between 1990 and 1993, all the participants were interviewed at their home, and 7,151 were examined at the research center to obtain baseline measurements, including a 10-second, 12-lead, resting electrocardiogram (ECG). Those who did not visit the research center were in general dependent or lived in nursing homes. The participants were reexamined during 2 follow-up rounds. The first follow-up examination was performed between July 1, 1993, and December 31, 1994. The second follow-up examination started April 1, 1997, and ended December 31, 1999. The Rotterdam Study collaborates with the general practitioners (GPs) and with the pharmacies in the area of Ommoord. The medical ethics committee of Erasmus University, Rotterdam, approved the study, and all participants gave informed consent.

ASSESSMENT OF THYROID STATUS

In 2002, we randomly selected 2,000 participants of the Rotterdam Study cohort who visited the research center at baseline. In 1,877 participants, baseline serum samples stored at –80°C were available and TSH levels were measured with a commercial TSH assay (Lumitest; Henning, Berlin, Germany [currently Brahms, Berlin]). In 2007, the serum FT₄ concentrations were measured (Vitros ECI Immunodiagnostics System; Ortho-Clinical Diagnostics, Amersham, England) in 1,544 participants for whom stored baseline blood samples were still available. The Spearman correlation coefficient of TSH between measurements 3 years apart, in different samples, was 0.71 (P < .01), suggesting reasonable stability over time. In 42 participants, the FT₄ concentrations were measured twice, in 2000 and in 2007, in the same blood samples. The Spearman correlation coefficient was 0.81 (P < .001), suggesting the limited effects of storage over time. The reference ranges of TSH (0.4-4.0 mU/L) and FT₄ (0.86-1.94 ng/dL [to convert to picomoles per liter, multiply by 12.871]) were the same as those used in previous studies on thyroid function in the Rotterdam Study and were based on the normal range of the assays. The Spearman correlation coefficient between TSH and FT₄ was –0.27 (P = .01).

DIAGNOSIS OF ATRIAL FIBRILLATION

New cases of atrial fibrillation were ascertained using 3 methods: (1) At baseline and during follow-up examinations, ECGs were recorded with an electrocardiograph (ACTA; Esaote, Florence, Italy), stored digitally, and analyzed by the Modular ECG Analysis System (MEANS). The reported sensitivity and specificity of the MEANS program in coding arrhythmias is high (96.6% and 99.3%, respectively). To verify the diagnosis of atrial fibrillation, all ECGs with a diagnosis of atrial fibrillation, atrial flutter, or any other rhythm disorder were recoded independently by 2 research physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was sought and taken as decisive in those cases in which disagreement persisted between the coding physicians. (2) General practitioners participating in the Rotterdam Study sent computerized information on selected diseases to the researchers of the Rotterdam Study sent computerized information on selected diseases to the researchers of the Rotterdam Study on a weekly basis. Specially trained follow-up assistants verified the information using GP records and the hospital discharge letters. A senior physician (J.H.) examined all the information and coded the events according to the International Statistical Classification of Diseases, 10th Revision (code I48). (3) Data on atrial fibrillation were acquired from the Dutch National Medical Registration (known as the LMR [de Landelijke Medische Registratie]) system, which accumulates all hospital discharge diagnoses of Dutch inhabitants. To ascertain atrial fibrillation at baseline, we used ECGs as described above. Furthermore, the GP files of all participants were screened for the presence of atrial fibrillation at or before baseline. We did not distinguish between atrial fibrillation and atrial flutter when we identified cases, because both conditions are very similar with respect to risk factors and consequences.19,20 Also, we did not discriminate between paroxysmal atrial fibrillation and chronic atrial fibrillation. It has been demonstrated that the frequency of periods of atrial fibrillation in paroxysmal atrial fibrillation as measured by continuous monitoring is much higher than the frequency perceived by patients and their physicians. In addition, paroxysmal atrial fibrillation changes into chronic atrial fibrillation over time in the majority of cases.21,22 Those patients who developed atrial fibrillation during a serious disease, resulting in death very shortly after the detection of atrial fibrillation, which was not the cause of the serious disease, were not considered as having atrial fibrillation. They were censored on the date of detection of atrial fibrillation. Furthermore, subjects with transient atrial fibrillation during myocardial infarction or during cardiac operative procedures were not included among the cases. All study participants were followed up from the day of entrance in the Rotterdam Study (1990-1993) to the date of onset of atrial fibrillation, to the date of death, or to January 1, 2000, whichever came first. If atrial fibrillation was detected exclusively by the MEANS computer system during 1 of the follow-up rounds, the midpoint between the date of the center visit of the concerning round and the date of the center visit of the former round was taken as the date of onset of atrial fibrillation. If atrial fibrillation was detected as well, or only, by the 2 other workup protocols, the earliest date was taken as the date of onset. By January 1, 2000, follow-up was complete for 99.1% of the study population.

MEASUREMENT OF COVARIATES

Information on medical history, smoking, and medication was obtained using the computerized questionnaire taken at the baseline home visit. The information on medication obtained from the home interview was completed by the computerized information from collaborating pharmacies. Participants were classified as current smokers, former smokers, or never smokers. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured twice at the right upper arm with a random-zero mercury sphygmomanometer with the participant in the sitting position. Systolic and diastolic blood pressures were calculated as the average of the 2 consecutive measurements. Hypertension was defined as a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 100 mm Hg or higher or the use of blood pressure–lowering drugs prescribed for hypertension, encompassing grades 2 and 3 hypertension, according to World Health Organization criteria. A history of myocardial infarction was confirmed by a review of the medical records of GPs and specialists. Assessment of heart failure at baseline in the Rotterdam Study has been described in detail previously. In short, heart failure cases were classified in accordance with the guidelines of the European Society of Cardiology based on the presence of at least 2 symptoms of heart failure (shortness of breath, ankle swelling, and pulmonary crepitations) or on the use of medication (diuretics, glycosides, or angiotensin-converting enzyme inhibitors) prescribed for the indication of heart failure in combination with objective evidence of cardiovascular disease. Data from the hospital discharge diagnoses database and from the GP files were used to complete this information. Left ventricular hypertrophy was diagnosed...
by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization. Diabetes was defined as the use of antidiabetic medication or a random or post-load serum glucose level of 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or higher. Serum total cholesterol was measured with an automated enzymatic method.

**VITAL STATUS**

Information on vital status was obtained on a regular basis from the Central Register of Population of the municipality of Rotterdam from collaborating GPs and by collecting information during follow-up rounds. For the participants for whom information remained missing, the Central Registry of Genealogy of the Netherlands was consulted. This national institute receives population registry records of those inhabitants of the Netherlands who have died.

**POPULATION FOR ANALYSIS**

For the present study, serum TSH samples were available from 1877 participants of the Rotterdam Study. We excluded 71 persons with prevalent atrial fibrillation and 79 participants for whom information on atrial fibrillation at baseline was missing. We also excluded 130 persons with a serum TSH level of less than 0.4 mU/L, 177 persons with a serum TSH level greater than 4.0 mU/L, and 55 persons who used thyrostatics (n=11), thymirometics (n=40), and/or amiodarone (n=9). The population for analysis consisted of 1426 subjects. Serum FT4 measurements were available in 1196 of the 1426 subjects. Based on serum FT4 levels outside the normal range (FT4 < 0.86 ng/dL and >0.94 ng/dL), 19 subjects were excluded for analysis of FT4, resulting in a secondary study population of 1177 persons.

**STATISTICAL ANALYSIS**

Age- and sex-adjusted hazard ratios (HRs) along with their 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model, with incident atrial fibrillation as the dependent variable and serum levels of TSH and FT4, respectively, as the independent variables. Serum TSH and FT4 levels were categorized into quartiles. In the analyses, the highest quartile of TSH and the lowest quartile of FT4 were used as the reference categories. Additional adjustments were made for current smoking, former smoking, body mass index, systolic blood pressure, hypertension, history of a myocardial infarction at baseline, presence of heart failure at baseline, left ventricular hypertrophy on the ECG, diabetes mellitus, total cholesterol level, and the time of the drawing of the blood sample. We calculated P for trend using TSH and FT4 as continuous variables. The Grambsch-Therneau test was used to test the validity of the proportional hazards assumption in all models used (which was found to be the case). Calculations for this purpose were made with Stata statistical software (Stata Corp, College Station, Texas). The numbers of missing values of covariates were low (≤1%). Missing values for cardiovascular risk factors were imputed using the expectation-maximization algorithm. Because of low numbers, we did not stratify the analyses by sex. Data were managed and analyzed using SPSS version 11.0 (SPSS Inc, Chicago, Illinois) and Stata version 8.

**RESULTS**

The characteristics of the study population are shown in Table 1. In this population of euthyroid participants, we identified 105 cases of atrial fibrillation (7.4%) based on the normal range of TSH during a median follow-up time of 8 years (range, 0.3-10.5 years). After adjustment for age and sex, subjects in the first quartile of TSH had an increased risk of atrial fibrillation compared with subjects in the lowest quartile (HR, 1.97; 95% CI, 1.15-3.38; P for trend,.02) (Table 2). Additional adjustments did not change the associations (Table 2). In participants with values in the normal range of TSH and FT4, a graded association of FT4 and the risk of atrial fibrillation was found (HR, 1.73; 95% CI, 0.91-3.28, highest quartile compared with lowest quartile; P for trend, .05) (Table 3). The associations were slightly lower after additional adjustments, and the P value for trend lost statistical significance (HR, 1.62; 95% CI, 0.84-3.14; P for trend,.06).

**COMMENT**

We report the findings of the first (to our knowledge) prospective population-based study on the association between normal thyroid function and risk of atrial fibrillation. We found that participants in the lowest quartile of the normal range of serum TSH had an almost 2-fold increased risk of atrial fibrillation compared with those who were in the highest quartile. Furthermore, we found a graded association between levels of FT4 and risk of atrial fibrillation.

Overt hyperthyroidism is a well-known risk factor for atrial fibrillation.8,9,24 Also, subclinical hyperthyroidism, defined as a low TSH level (≤0.1 mU/L), with a serum FT4 concentration within the normal range, has also been identified as a causal condition for atrial

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Table 1. Baseline Characteristics of 1455 Participants in the Rotterdam Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.4 (7.5)</td>
</tr>
<tr>
<td>Proportion of men, %</td>
<td>41</td>
</tr>
<tr>
<td>TSH, mU/L</td>
<td>1.66 (0.81)</td>
</tr>
<tr>
<td>FT4, pmol/L</td>
<td>16.2 (3.0)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.4 (3.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138 (21)</td>
</tr>
<tr>
<td>Serum total cholesterol level, mmol/L</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>32.9</td>
</tr>
<tr>
<td>Never smokers</td>
<td>32.8</td>
</tr>
<tr>
<td>Current smokers</td>
<td>43.3</td>
</tr>
<tr>
<td>Former smokers</td>
<td>43.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9.8</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>12.3</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on the ECG, %</td>
<td>3.2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>32</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECG, electrocardiogram; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Conventional unit conversion factors: To convert FT4 to nanograms per deciliter, divide by 0.0259. To convert FT4 to nanograms per milligram per deciliter, divide by 0.0259.

Continuous variables are expressed as mean (SD).

Subjects (n=1177) with FT4 levels within the normal range (11-25 pmol/L).
The level of serum FT₄ is tightly regulated by the classical hypothalamic-pituitary-thyroid axis. Three pathways are involved in the effects of thyroid hormone on the heart. The active thyroid hormone triiodothyronine (T₃) binds to the T₃ nuclear receptors, resulting in specific cardiac gene expression. Furthermore, T₃ influences the sensitivity of the peripheral sympathetic system, and, finally, T₃ affects the peripheral hemodynamic state, leading to increased cardiac filling, which affects cardiac contraction patterns. Excess of thyroid hormone causes arrhythmias, peripheral vasodilatation, and changes in cardiac contractility. Each person probably has his or her own individual set point for thyroid function. Genetic factors play an important role in the set point of the hypothalamic-pituitary-thyroid axis. In a Danish study, the individual reference ranges for test results in a healthy group of young males was very narrow, while the group reference range for thyroid function test results was much wider. The results of our study indicate that within the normal range of thyroid function certain persons are nonetheless at increased risk for developing atrial fibrillation. It could be hypothesized that low levels of serum TSH have a nonthyroidal reason. It is known that critical illness may cause a decrease in the level of TSH. Chronic diseases of the elderly, causing both atrial fibrillation and a low TSH level, could have confounded the association of a low TSH level with atrial fibrillation. We believe that this is not the case in our study. First, the participants were able to come to our research center and therefore belonged to the healthier part of the Rotterdam Study population. Second, the results of the secondary analysis revealed that both lower levels of TSH and higher levels of FT₄ were associated with atrial fibrillation, indicating that the effect, indeed, is thyroidal as low levels of TSH in the case of critical illness go together with low levels of FT₄.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases/Subjects</th>
<th>HR (95% CI), Model 1</th>
<th>HR (95% CI), Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH, range, mU/L</td>
<td>105/1426</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile, 0.4-1.04</td>
<td>39/358</td>
<td>1.97 (1.15-3.38)</td>
<td>1.94 (1.13-3.34)</td>
</tr>
<tr>
<td>Second quartile, 1.05-1.51</td>
<td>20/356</td>
<td>1.01 (0.54-1.87)</td>
<td>1.06 (0.57-1.99)</td>
</tr>
<tr>
<td>Third quartile, 1.52-2.16</td>
<td>26/355</td>
<td>1.29 (0.72-2.31)</td>
<td>1.34 (0.75-2.41)</td>
</tr>
<tr>
<td>Fourth quartile, 2.17-3.98</td>
<td>20/357</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value for trend</td>
<td></td>
<td>.02</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

4 The study participants (N=1426) had serum TSH levels within the normal range (0.4-4.0 mU/L) and did not use amiodarone and/or thyroid medication.

5 Adjusted for age and sex.

6 Adjusted for age, sex, current smoking, former smoking, body mass index, systolic blood pressure, hypertension, history of a myocardial infarction at baseline, presence of heart failure at baseline, left ventricular hypertrophy on the electrocardiogram, diabetes mellitus, total cholesterol level, and time of the drawing of the blood sample.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases/Subjects</th>
<th>HR (95% CI), Model 1</th>
<th>HR (95% CI), Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT₄, pmol/L</td>
<td>83/1177</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile, 11.0-14.4</td>
<td>15/297</td>
<td>1.01 (Reference)</td>
<td>1.01 (Reference)</td>
</tr>
<tr>
<td>Second quartile, 14.5-15.9</td>
<td>20/289</td>
<td>1.40 (0.72-2.74)</td>
<td>1.29 (0.65-2.52)</td>
</tr>
<tr>
<td>Third quartile, 16.0-17.9</td>
<td>23/296</td>
<td>1.58 (0.83-3.04)</td>
<td>1.51 (0.78-2.90)</td>
</tr>
<tr>
<td>Fourth quartile, 18.0-25.0</td>
<td>25/295</td>
<td>1.73 (0.91-3.28)</td>
<td>1.62 (0.84-3.14)</td>
</tr>
<tr>
<td>P value for trend</td>
<td></td>
<td>.05</td>
<td>.06</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

Conventional conversion factor: To convert FT₄ values to nanograms per deciliter, divide by 12.871.

A recently published cross-sectional study revealed that in euthyroid persons, defined by TSH within the normal range, serum FT₄, but not TSH, is associated with atrial fibrillation. In our prospective study, we also found that, within the euthyroid range, those who have higher levels of thyroid function are at an increased risk of atrial fibrillation compared with those who have lower levels. In our study, in contrast with the study of Gammage et al., TSH levels within the normal range were clearly associated with the risk of atrial fibrillation. The active thyroid hormone triiodothyronine (T₃) binds to the T₃ nuclear receptors, resulting in specific cardiac gene expression. Furthermore, T₃ increases the sensitivity of the peripheral sympathetic system, and, finally, T₃ affects the peripheral hemodynamic state, leading to increased cardiac filling, which affects cardiac contraction patterns. Excess of thyroid hormone causes arrhythmias, peripheral vasodilatation, and changes in cardiac contractility. Each person probably has his or her own individual set point for thyroid function. Genetic factors play an important role in the set point of the hypothalamic-pituitary-thyroid axis. In a Danish study, the individual reference ranges for test results in a healthy group of young males was very narrow, while the group reference range for thyroid function test results was much wider. The results of our study indicate that within the normal range of thyroid function certain persons are nonetheless at increased risk for developing atrial fibrillation.
Based on the results of our study, we are unable to conclude that high thyroid function is a risk factor for atrial fibrillation or that low thyroid function is protective against atrial fibrillation. To the best of our knowledge, hypothyroidism has never been associated with atrial fibrillation, in contrast to hyperthyroidism. Therefore, we believe that the best explanation of our results is that high thyroid function within the normal range is associated with atrial fibrillation.

The strengths of our study are the population-based setting and its longitudinal character, through which we were able to give evidential value to earlier cross-sectional findings. Some weaknesses also need to be mentioned. When we measured FT₄ in stored samples in 2007, we were unable to obtain samples from the same number of participants for whom TSH had been measured in 2002. The more limited availability of blood samples at a later time might reflect the mechanism that serum samples of participants who are not very healthy at baseline or at early follow-up visits are depleted owing to more intensive use for cross-sectional and case-control studies. A selection of healthy participants for the analysis of FT₄ could be the result. We analyzed the associations of TSH and risk of atrial fibrillation in the original TSH sample (n=1426) and in the sample for which a FT₄ measurement was also available (n=1177) and concluded that the associations were almost identical. Therefore, we believe that this potential selection has not influenced the results. In our study, we measured FT₄ as a marker of the active hormone. Measurements of T₃ and free T₃ need a considerable amount of serum, and population-based studies are restricted in this respect.

It is generally believed that there are reasons to reconsider the normal range of TSH levels. Most discussion, however, is on the upper limit of TSH, indicating that the upper normal limit should be decreased to 2.5 mU/L. The lower limit of TSH is less debated. Our data indicate that in persons whose thyroid function is within the normal range a subgroup may be found at higher risk of atrial fibrillation owing to increased thyroid function. The observational character of our study, however, precludes a judgment on causality, and whether the relationship is causal has to be determined in other studies. Of interest, in populations with normal thyroid function, associations of thyroid function with bone status and physical activity have been reported.

It is known that atrial fibrillation resulting from overt hyperthyroidism is reverted in 60% to 75% of the patients if they receive proper antithyroid treatment. Whether patients with atrial fibrillation and high normal thyroid function also easily revert to sinus rhythm if they are treated as if they were hyperthyroid also needs to be investigated. In conclusion, within the normal range of serum thyroid function parameters, subjects with high-normal thyroid function are at an increased risk of atrial fibrillation. This finding requires confirmation in other studies.

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Author Contributions: Drs Heeringa and Hoogendoorn contributed equally to this article. Study concept and design: Heeringa, Hoogendoorn, van der Deure, Hofman, Peeters, den Heijer, Visser, and Witteman. Acquisition of data: Heeringa, van der Deure, and Visser. Analysis and interpretation of data: Heeringa, Hoogendoorn, van der Deure, Peeters, Hop, den Heijer, Visser, and Witteman. Drafting of the manuscript: Heeringa, Hoogendoorn, and Peeters. Critical revision of the manuscript for important intellectual content: Heeringa, van der Deure, Hofman, Peeters, Hop, den Heijer, Visser, and Witteman. Obtained funding: Hofman and Witteman. Administrative, technical, and material support: Heeringa, van der Deure, Peeters, and Visser. Study supervision: Hofman and Witteman.

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