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Arterial stiffness and subclinical atherosclerosis in the coronary arteries at different stages of dysglycaemia

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Abstract

Aim: Our aim was to investigate in a large population-based cohort study whether increased arterial stiffness and subclinical atherosclerosis in the coronary arteries differ at different stages of dysglycaemia.

Methods: Data were obtained from SCAPIS, a population-based cohort of participants 50–64 years. The study population of 9379 participants was categorised according to glycaemic status: normoglycaemic, pre-diabetes (fasting glucose: 6.1–6.9 mmol/L and/or HbA1c 6%–6.4%) and diabetes. Pulse wave velocity (PWV) was measured by the SphygmoCor XCEL system and arterial stiffness was defined by PWV ≥10 m/s. Coronary artery calcium score (CACS) was assessed by coronary computed tomography and coronary artery calcification was defined by CACS ≥100.

Results: We identified 1964 (21%) participants with dysglycaemia, out of which 742 (7.9%) had diabetes mellitus. PWV ≥10 m/s was present in 808 (11%), 191 (16%), 200 (27%) and CACS ≥100 in 801 (11%), 190 (16%), 191 (28%) participants with normoglycaemia, pre-diabetes and diabetes, respectively, all, p < 0.001. The overlap between PWV ≥10 m/s and CACS ≥100 within each glycaemic category was 188 (2.5%), 44 (3.6%) and 77 (10) respectively. There was an association between glycaemic status and increased PWV in the fully adjusted models, but not for glycaemic status and CACS ≥100, where there was no difference for pre-diabetes compared to normoglycaemia, OR 1.2 (95% CI 0.98–1.4). In the total study population, there was an association between HbA1c and PWV after adjustment, p < 0.001. The overlap between markers of major subclinical vascular damage was small in all glycaemic categories. This could be explained by different pathways in the pathogenesis of arterial stiffness or atherosclerosis in the coronary arteries.

Conclusions: Our results show that increased arterial stiffness and subclinical coronary artery atherosclerosis are present in the early stages of dysglycaemia, but the overlap between markers of major subclinical vascular damage was small in all glycaemic categories. This could be explained by different pathways in the pathogenesis of arterial stiffness or atherosclerosis in the coronary arteries.

Keywords
arterial stiffness, coronary artery calcium score, pre-diabetes, pulse wave velocity

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1 | INTRODUCTION

Both type 1 and type 2 diabetes are known risk factors for cardiovascular disease (CVD). Type 2 diabetes is usually preceded by a pre-diabetic state characterised by elevated blood glucose levels, that is, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), which confer an increased risk of cardiovascular disease and subclinical vascular damage. From previous research in this area, we know that diabetes and pre-diabetes have increased atherosclerosis in the coronary arteries, as measured by the coronary artery calcification score (CACS), compared to normoglycaemic individuals.

Aortic arterial stiffness as a result of biological ageing and arteriosclerosis, is characterised by higher intravascular distending pressure and has been recognised as a marker of CVD and all-cause mortality in various populations. Furthermore, increased arterial stiffness is associated with several established CVD risk factors such as central obesity, low physical activity, type 2 diabetes and masked nocturnal hypertension in type 2 diabetes. However, in relation to pre-diabetes, the results of different studies vary. Depending on which definition of dysglycaemia is used, IGT, IFG or elevated HbA1c, different results have been presented in relation to cardiovascular disease and prevalent arterial stiffness.

The aim of this study was to determine the prevalence and overlap of asymptomatic vascular organ damage, defined by arterial stiffness and coronary artery atherosclerosis, in individuals with diabetes and pre-diabetes compared with normoglycaemic individuals using the large population-based Swedish CArdioPulmonary bio-Image Study (SCAPIS).

2 | MATERIALS AND METHODS

2.1 | Subjects

Data on arterial stiffness were collected as part of a local substudy of SCAPIS, a joint research project of six Swedish universities, Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå and Uppsala. The SCAPIS recruitment phase was completed in November 2018 with 30,154 subjects aged 50–64 years. Pulse wave velocity (PWV) was measured as a local substudy in Malmö and in Linköping. From the population of Malmö, 6251 subjects participated in the SCAPIS study, the participation rate in Malmö was 53%. From the population of Linköping, 5057 persons participated and the participation rate was 58%. The study adhered to the strengthening of the reporting of observational studies in epidemiology, STROBE guidelines. SCAPIS was approved by the Regional Ethical Review board in Umeå (Dnr 2010-228-31M) and the Regional Ethical Review board in Linköping (Dnr 2018/478-31) and adheres to the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2 | Measurements of cardiovascular risk factors and covariates

Detailed information on self-reported health, medication, family history, lifestyle, smoking habits, psychosocial well-being, occupational and environmental exposure, social determinants such as socio-economic status was obtained from a questionnaire. After an overnight fast a venous blood sample was collected for analysis of plasma glucose, HbA1c, total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, creatinine and high-sensitivity C-reactive protein (CRP).

2.3 | Coronary artery calcification

Coronary artery calcification was assessed in noncontrast-enhanced images from a state-of-the-art multi-slice computed tomography scanner (Siemens, Somatom Definition Flash, Siemens Healthineers,
Erlangen, Germany). Imaging and analyses were performed using a calcium scoring protocol and the calcium content in each coronary artery was measured and summed to produce a total coronary artery calcification score (CACS) according to international standards.17,18 An Agatston score ≥ 100 was defined as having coronary artery calcification.

2.4 Pulse wave velocity

The arterial stiffness data presented here include 3448 participants studied at Linköping University Hospital, Linköping, Sweden, between 2014 and 2018, and 5965 participants studied at Skåne University Hospital, Malmö, Sweden.

Carotid-femoral PWV, the current reference method for assessing arterial stiffness,19 was used to determine arterial stiffness and was measured using the SphygmoCor Xcel applanation tonometer (Atcor Medical, Australia). Prior to the examination, participants were instructed to abstain from caffeine and a heavy meal for 3 h, nicotine for 4 h and alcohol for 12 h. Blood pressure cuffs were placed on the left upper arm and right thigh (10–20 cm below the groin). The distance between the femoral pulse and the upper edge of the thigh cuff was subtracted from the distance between the carotid receptor and the upper edge of the thigh. The PWV was calculated as

\[ \text{PWV} = \frac{D_2 - D_1}{T} \]

where

- \( D_2 \) is the distance between the carotid receptor and the upper edge of the thigh cuff,
- \( D_1 \) is the distance between the femoral pulse and the upper edge of the thigh cuff,
- \( T \) is the determined transit time between the carotid and femoral pulse.

The PWV was expressed in m/s. The PWV was considered elevated when ≥10 m/s.18

A logistic regression was used for assessing PWV as predictor for CACS ≥100, adjusted for glycaemic status. Venn diagrams were used to illustrate PWV ≥10 m/s and CACS ≥100 when comparing the different glycaemic groups and prevalent impaired fasting glucose and elevated HbA1c in the pre-diabetes group as well. Sensitivity analyses of participants with pre-diabetes subgrouped as IFG and/or elevated HbA1c were compared to those with normoglycaemia in separate logistic models.

2.5 Glycaemic status

The study population was categorised according to glycaemic status: normoglycaemic (glucose: <6.1 mmol/L and HbA1c <42 mmol/mol (<6.0%)), pre-diabetes defined as impaired fasting (glucose: 6.1–6.9 mmol/L and/or elevated HbA1c 42–47 mmol/mol (6.0%–6.4%)) and diabetes mellitus (glucose ≥7.0 mmol/L and/or HbA1c ≥48 mmol/mol (>6.5%) or previously known diabetes).

2.6 Statistical methods

Categorical variables were summarised as the number of patients with corresponding percentage. Continuous variables were summarised as mean (SD) or, for those with a skewed distribution, median (interquartile range). Variables were visually categorised as normally distributed or skewed. Mean values comparison was calculated using an ANOVA test, with normoglycaemia, pre-diabetes and diabetes as subgroups. Skewed variables were compared by use of a Kruskal–Wallis test. For comparison of categorical variables, we used a chi-square test. A boxplot was created for the groups with normoglycaemia, pre-diabetes and diabetes with PWV plotted for each group. Furthermore, a scatterplot was plotted with PWV as dependent variable and HbA1c as nondependent. Odds ratios and corresponding 95% confidence intervals for PWV were calculated by use of logistic regression analysis, where participants with diabetes were compared to those with normoglycaemia as well as those with pre-diabetes in separate models. Participants with pre-diabetes were also compared to participants in the normoglycaemic group. The logistic regression analyses were both crude and adjusted; the full model was adjusted for age, sex, systolic blood pressure, BMI, coronary calcium score CACS ≥100, LDL-cholesterol, smoking, pulse, site and CRP. A logistic regression was to evaluate PWV continuously as a predictor for CACS ≥100, adjusted for glycaemic status. Venn diagrams were used to illustrate PWV ≥10 m/s and CACS ≥100 between the different glycaemic groups and prevalent impaired fasting glucose and elevated HbA1c in the pre-diabetes group as well. Sensitivity analyses of participants with pre-diabetes subgrouped as IFG and normoglycaemic HbA1c; elevated HbA1c and normoglycaemic fasting glucose and both elevated HbA1c and IFG were compared to those with normoglycaemia in separate logistic models.

3 RESULTS

There were 9413 participants from Malmö and Linköping with complete PWV data. Of these, 9379 participants also had data that allowed classification of glycaemic status, out of whom 7415 (79%) were normoglycaemic, 1222 (13%) were classified as having pre-diabetes and 742 (7.9%) were classified as having diabetes, Figure 1. Table 1 shows baseline characteristics for traditional cardiovascular risk factors, PWV and CACS stratified for different glycaemic status. Tables 2a and 2b shows the odds ratio per 1 m/s increase in PWV and CACS ≥100 when comparing the different glycaemic status groups with each other, adjusted for CVD risk factors in the full model. All differences were statistically significant but OR adjusted for CACS ≥100 when comparing pre-diabetes versus normoglycaemia in the full model.

In Figure 2a, the Venn diagram shows the prevalence of PWV ≥10 m/s and/or CACS ≥100 among participants in the three groups with different glycaemic status. Furthermore, there was an independent association between PWV as predictor for CACS ≥100 when adjusted for the glycaemic categories, OR 1.4 (95% CI 1.3–1.4). Figure 2b illustrates the different domains of pre-diabetes categorised by IFG and/or elevated HbA1c.
As shown, most of the pre-diabetes group were identified by IFG. In the sensitivity analyses of pre-diabetes, there was an association between the IFG subgroup and the elevated HbA1c subgroup with CACS \( \geq 100 \) in the fully adjusted model. For PWV, there was an association for the IFG subgroup in the fully adjusted model, but not for the elevated HbA1c subgroup, Supplementary Table S1.

Figure 3 shows a scatter plot illustrating the association between PWV and HbA1c level as a continuous variable in the entire study population. The association between HbA1c and PWV (dependent) was further investigated after adjustment in a linear regression, \( 0.030 \) (95% CI 0.026–0.034). PWV increased significantly with increasing severity of dysglycaemia, as shown, Supplementary Figure S1.

4 | DISCUSSION

In this study, PWV and CACS were used in a large, randomly selected sample of the general population to define subclinical vascular damage in normoglycaemic individuals compared with individuals with pre-diabetes or diabetes. We found that aortic arterial stiffness and coronary artery atherosclerosis were more common in people with diabetes and pre-diabetes than in normoglycaemic individuals. However, the overlap between markers of major subclinical vascular damage was small in all glycaemic categories.

PWV reflects the effects of hypertension on the vessel wall, and a high-velocity pulse wave indicates stiffer arteries.\(^7,20,21\) It is widely believed that elevated glucose levels and hyperinsulinaemia can trigger cascade responses throughout the body, leading to remodelling of the vascular bed and accelerated progression of atherosclerosis.\(^22,23\) More specifically, one of the main mechanisms of hyperglycaemia affecting arterial stiffness is the formation of advanced glycation end products.\(^24\) There is ample evidence of the prognostic value of vascular stiffness in predicting cardiovascular events. However, arterial stiffness and atherosclerosis are distinct processes from a mechanistic and pathological perspective,\(^25\) both representing damage to vascular organs that sometimes occur together. However, the overlap of these different entities of vascular organ damage in normoglycaemic individuals compared to patients with different stages of dysglycaemia has not yet been studied.

4.1 | Comparison with other studies

Type 2 diabetes is a known risk factor for macrovascular disease and subclinical organ damage, for example, defined by calcification of the coronary arteries. As far as pre-diabetes is concerned, the results of different...
studies vary. In most studies, pre-diabetes was associated with increased CACS compared to normoglycaemic participants. However, in one study where pre-diabetes was defined by IFG only, there was no such association after adjustment, which is consistent with our findings. A previous study found that increased arterial stiffness was present in individuals with pre-diabetes defined by increased HbA1c and IGT, but not in those with IFG. We could not confirm this, our results showed that pre-diabetes was associated with arterial stiffness in participants with both IFG and increased HbA1c. There was a borderline significant association for participants with IFG alone with arterial stiffness, but not for participants with elevated HbA1c alone. Furthermore, the prevalence

### TABLE 1 Baseline characteristics for 9379 participants from Malmö and Linköping, Sweden, in the SCAPIS cohort study by different categories of glycaemic status.

<table>
<thead>
<tr>
<th>Category</th>
<th>Normoglycaemia n = 7415</th>
<th>Pre-diabetes n = 1222</th>
<th>Diabetes n = 742</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women – n (%)</td>
<td>4010 (54)</td>
<td>582 (48)</td>
<td>271 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age – mean (SD)</td>
<td>57.2 (4.3)</td>
<td>58.1 (4.3)</td>
<td>58.9 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers – n (%)</td>
<td>996 (13.4)</td>
<td>218 (17.8)</td>
<td>123 (16.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoke duration – Median (Q2–Q4)</td>
<td>25 (13–38)</td>
<td>30 (17–41)</td>
<td>31 (17–41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol – mean (SD)</td>
<td>5.6 (1.0)</td>
<td>5.3 (1.1)</td>
<td>4.7 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol – mean (SD)</td>
<td>3.6 (0.9)</td>
<td>3.4 (1.0)</td>
<td>2.9 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP – Median (Q2–Q4), mg/L</td>
<td>1 (0.6–2)</td>
<td>1.4 (0.65–3.2)</td>
<td>1.7 (0.8–3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure – mean (SD), mmHg</td>
<td>126 (17)</td>
<td>130 (17)</td>
<td>132 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure – mean (SD), mmHg</td>
<td>78 (11)</td>
<td>80 (11)</td>
<td>80 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist Circumference – mean (SD) cm</td>
<td>92 (12)</td>
<td>99 (13)</td>
<td>104 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body Mass Index – Median (Q2–Q4), kg/m²</td>
<td>26 (24–29)</td>
<td>28 (25–31)</td>
<td>29 (27–33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse – mean (SD), BPM</td>
<td>60 (9)</td>
<td>63 (10)</td>
<td>66 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWV – mean (SD), m/s</td>
<td>8.4 (1.3)</td>
<td>8.8 (1.4)</td>
<td>9.3 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWV≥10 m/s – n (%)</td>
<td>808 (10.9)</td>
<td>191 (15.6)</td>
<td>200 (27.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWV≥10 m/s + CACS≥100 – n (%)</td>
<td>188 (2.5)</td>
<td>44 (3.6)</td>
<td>77 (10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CACS≥100 – n (%)</td>
<td>801 (11.1)</td>
<td>190 (16.4)</td>
<td>191 (27.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CACS≥400 – n (%)</td>
<td>231 (3.2)</td>
<td>69 (6.0)</td>
<td>89 (12.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: There were few missing data, less than 10 (0.1%) for all variables except for CACS, where data were missing for 284 (3.0%) participants and LDL where data were missing for 53 (0.6%) participants. Data are as follows: Mean values (SD), Median (Q2-Q4) and numbers (%) for normoglycaemic, pre-diabetes and diabetes as subgroups. Normally distributed variables were compared using an ANOVA test, skewed variables were compared by use of a Kruskal–Wallis test and categorical variables were compared by a chi-square test.

Abbreviations: CACS ≥100, coronary artery calcium score ≥100; CRP, C-reactive protein; LDL, low-density lipoprotein cholesterol; PWV, pulse wave velocity; SCAPIS, Swedish CardioPulmonary bioImage Study.

### TABLE 2A Odds ratio per 1 m/s increment of pulse wave velocity (PWV) in participants with normoglycaemia, pre-diabetes or diabetes.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes vs. normoglycaemia</th>
<th>Pre-diabetes vs. normoglycaemia</th>
<th>Diabetes vs. pre-diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Crude model</td>
<td>1.5 (1.4–1.6)</td>
<td>1.2 (1.2–1.3)</td>
<td>1.3 (1.2–1.3)</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.4 (1.3–1.5)</td>
<td>1.2 (1.1–1.2)</td>
<td>1.2 (1.1–1.3)</td>
</tr>
<tr>
<td>Adjusted for age, sex, systolic blood pressure, waist, CACS≥100, LDL, smoking status, pulse, CRP and site</td>
<td>1.3 (1.2–1.4)</td>
<td>1.1 (1.0–1.2)</td>
<td>1.1 (1.0–1.2)</td>
</tr>
</tbody>
</table>
of increased arterial stiffness and coronary artery calcification was almost identical within each of the glycaemic categories. However, the overlap of arterial stiffness and coronary artery calcification was small. This result is supported by the independent association between glycaemic status and PWV after adjustment for CACS. This could therefore be due to different pathways or individual differences in susceptibility to hyperglycaemia in the mechanisms involved in the remodelling of the arterial wall and subsequent progression of arterial stiffness compared to plaque calcification in the coronary arteries.\(^\text{25}\)

Some studies\(^\text{27}\) have failed to show that IFG is a risk factor for CVD, while other studies have shown that IFG is a risk factor for CVD.\(^\text{12}\) In our pre-diabetes group, only a fraction of participants had both IFG and elevated HbA1c, while the majority had isolated IFG. The finding that the pre-diabetes group had a significantly higher PWV than the normoglycaemic group may suggest that CVD risk may be higher compared with normoglycaemic individuals, even when HbA1c is normal.

### 4.2 Strengths and Weaknesses

The greatest strength of this population-based cohort study is its sample size. More than 9000 randomly selected individuals were studied according to a common, standardised and detailed protocol, with data

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**TABLE 2B** Odds ratio for CACS$\geq$100 in participants in participants with normoglycaemia, pre-diabetes or diabetes.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes vs. normoglycaemia</th>
<th>Pre-diabetes vs. normoglycaemia</th>
<th>Diabetes vs. pre-diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Crude model</td>
<td>3.0 (3.5–3.7)</td>
<td>1.6 (1.3–1.9)</td>
<td>1.9 (1.5–2.4)</td>
</tr>
<tr>
<td>Adjusted for age and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td>2.2 (1.8–2.7)</td>
<td>1.4 (1.1–1.6)</td>
<td>1.6 (1.3–2.1)</td>
</tr>
<tr>
<td>Adjusted for age, sex, systolic blood pressure, waist, PWV, LDL, smoking status, pulse, CRP and site</td>
<td>1.8 (1.4–2.2)</td>
<td>1.2 (0.98–1.4)</td>
<td>1.6 (1.2–2.0)</td>
</tr>
</tbody>
</table>

Note: Normoglycaemia: glucose: <6.1 mmol/L and HbA1c 6% (<42 mmol/mol), $n$ = 7415. Pre-diabetes: impaired fasting glucose: 6.1–6.9 mmol/L and/or elevated HbA1c 6%–6.5% (42–47 mmol/mol), $n$ = 1222. Diabetes: glucose $\geq$7.0 mmol/L and/or HbA1c $>6.5%$ (48 mmol/mol) or previously known diabetes, $n$ = 742.

Abbreviations: CACS$\geq$100, coronary artery calcium score$\geq$100; CRP, C-reactive protein; LDL, low-density lipoprotein cholesterol.
from two vascular beds. Nevertheless, the study carries a risk of selection bias, and due to its observational and cross-sectional nature, we cannot establish causality. Regarding possible selection bias, we know from the SCAPIS pilot study that low socio-economic status was associated with lower participation rates. In addition, an association between living in an area of low socio-economic status and increased coronary artery calcification has been previously observed. Although pre-diabetes was defined here according to the guidelines of NICE, no information on glucose tolerance tests was available, so we could not include these data in our definition of pre-diabetes.

4.3 | Conclusions

In conclusion, our results show that increased arterial stiffness of the aorta is present in the early stages of dysglycaemia. The prevalence of arterial stiffness and coronary artery atherosclerosis was almost identical within each glycaemic category, but the overlap was small. This could be explained by different pathways in the pathogenesis of arterial stiffness or coronary artery atherosclerosis. Finally, true estimates of prevalence in the population are important if we are to develop and apply successful screening strategies. Our findings support the AHA/ACC guidelines, which recommend measurement of CACS in intermediate-risk adults to facilitate the conversation between physician and patient.

**AUTHOR CONTRIBUTIONS**

J.C., K.R. and C.J.Ö. contributed to the concept and rationale for the study, interpretation of the results and drafted the manuscript. J.C. conducted statistical analysis with advice from K.R. and C.J.Ö. J.C., K.R., I.F.M., G.E., J.E. and C.J.Ö contributed to discussion and reviewed and edited the manuscript. G.E. and C.J.Ö. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**CONFLICT OF INTEREST STATEMENT**

None.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES


SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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