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DOES PERIODONTITIS AFFECT DIABETES INCIDENCE AND HAEMOGLOBIN A1c CHANGE? AN 11-YEAR FOLLOW-UP STUDY

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ABSTRACT

Aim. – As periodontitis may contribute to the pathogenesis of diabetes, the effects of periodontitis on diabetes incidence and HbA1c change was quantified in a prospective cohort.

Methods. – Data from an 11-year follow-up of the Study of Health in Pomerania were analyzed to evaluate the effects of periodontitis on incident diabetes and long-term HbA1c changes in 2047 subjects aged 20–81 years. Diabetes was based on self-reported physician diagnoses, antidiabetic medication use, or HbA1c ≥ 6.5% or non-fasting blood glucose levels ≥ 11.1 mmol/L. To assess periodontal status, periodontal pockets were probed, and their depth and clinical attachment levels measured. For both measures, means and percentages of sites ≥ 3 mm were calculated. In addition, all probing depths ≥ 4 mm were summed (cumulative probing depth). Modified Poisson and multivariable linear models were applied, adjusted for age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status and follow-up time.

Results. – Over a mean follow-up period of 11.1 years, 207 subjects developed diabetes. Baseline mean clinical attachment levels (CALs) and probing depths (PPDs) were not significantly associated with either diabetes incidence [mean CALs, fourth quartile, incidence rate ratio = 0.819, 95% confidence interval (CI): 0.489–1.370; *P* = 0.446] or long-term changes in HbA1c (mean CALs, fourth quartile, β = -0.086, 95% CI: -0.187, -0.016; *P* = 0.098). Sensitivity analyses using alternative exposure definitions confirmed these results.

Conclusion. – Contrary to the currently available literature, no convincing evidence was found of any potential association between periodontitis and diabetes incidence or HbA1c change.

Keywords: Chronic periodontitis; Cohort studies; Diabetes mellitus; Haemoglobin A1c; Incidence; Progression; Study of Health in Pomerania

INTRODUCTION

Diabetes mellitus represents a major global health burden. Approximately 415 million people worldwide live with diabetes, and this number is expected to increase to 642 million by 2040 [1]. Over the next few decades, the prevalence of diabetes is likely to increase in the developed and especially the developing countries [2]. For this reason, examining other clinical conditions that may predispose to diabetes could have important public-health implications for early diabetes care and management.

Periodontitis is characterized by chronic infection and inflammation of tooth-supporting tissues [3]. Periodontal infection may cause systemic inflammation [4] *via* low-grade, continuous bacteraemia or by spillover of proinflammatory cytokines locally produced in the gingiva into the bloodstream [5, 6]. In turn, advanced glycation end-products (AGEs) are produced [7], which contribute to the onset of diabetes *via* increased dysregulation of metabolic control [8].

In recent years, the bidirectional association between diabetes and chronic periodontitis has received considerable attention [9, 10]. However, longitudinal epidemiological data describing the effects of periodontitis on the development of diabetes in the general population are scarce and have contributed to the current evidence only to a limited degree [11–14]. In the adult US population (aged 25–74; n = 9296) examined in the first National Health and Nutrition Examination Survey (NHANES) performed in the early 1970s, individuals with higher periodontal index categories exhibited greater odds of developing future diabetes [13]. On analyzing data from 2973 diabetes-free subjects in the Study of Health in Pomerania (SHIP) [15], participants in the highest periodontal disease category [as defined by quartiles (Q) of the percentage of sites with clinical attachment levels (CALs) ≥ 5 mm] had a 0.08% higher 5-year haemoglobin A1c (HbA1c) change compared with participants in the lowest periodontal disease

category. In an Asian retrospective cohort study (n = 22,299), those with periodontitis, as indicated by a need for surgery, exhibited a 1.19-fold higher incidence of diabetes than those without periodontitis matched from the general population [11]. Another study of 2469 male Japanese workers [12] revealed an increased relative risk [risk ratio (RR): 1.73] for incident type 2 diabetes (T2D) in those reporting tooth loss. In contrast, another study reported a non-significant association between moderate or severe periodontitis (using scores 3–4 of the Community Periodontal Index) and incident diabetes in a large (n = 5848) prospective 7-year follow-up study of Japanese adults [14]. While most of these studies were large-scale, they had serious limitations in terms of study design, exposure/outcome assessment and/or insufficient confounder adjustment, thereby limiting their contribution to the current evidence.

At present, there is no consensus on the case definition of chronic periodontitis [16, 17]. Thus, exposure/outcome effects were estimated using definitions favourable from an epidemiological and statistical point of view. Periodontal disease status is commonly assessed by current (pocket probing depth, PPD) and cumulative (CAL) disease measures. Using both measures, our present study evaluated the different definitions quantifying disease severity (mean) and extent (percentage of diseased sites) [18, 19]. In addition, the cumulative PPD, which quantifies current periodontal inflammation and is sensitive to reductions in inflammatory exposure, was also determined [20]. Exposure definitions were analyzed continuously, thereby reducing the chances of misclassification, and as Q1–Q4. By using various exposure definitions and parameters, the constancy of the potential exposure/outcome effects was thoroughly evaluated, thus strengthening the validity of our conclusions.

In light of the above facts, the effects of various baseline periodontitis definitions on incident diabetes in 2047 diabetes-free individuals were also examined using prospective data from the

population-based SHIP-0 and SHIP-2. In addition, the effects of periodontitis definitions on long-term changes in HbA1c levels were also assessed.

METHODS

Study population

The SHIP is an ongoing longitudinal population-based health survey in West Pomerania [21]. A two-stage cluster sampling method was adopted from the World Health Organization (WHO) Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project based in Augsburg, Germany [22]. Caucasian subjects of both genders with German citizenship and main residency in the study area were randomly sampled within 12 5-year age-based strata, each including 292 subjects. The remaining net sample (excluding the emigrated and deceased) comprised 6265 eligible subjects. In the end, 4308 subjects participated in the baseline examinations between 1997 and 2001 (SHIP-0). Of these, 3300 subjects participated in the 5-year SHIP-1 follow-up examinations during 2002–2006. Of the 3708 eligible individuals who participated in SHIP-0 and were also invited to participate in the 11-year follow-up, 2333 were ultimately examined between 2008 and 2012 (SHIP-2; 62.9% follow-up response) [23].

The study protocol was approved *a priori* by the Ethics Committee of the University of Greifswald, and written informed consent was obtained from each participant. This study was performed in accordance with 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)' guidelines for human research studies [24].

Detailed information on the non-responses, exclusion criteria, and number and type of missing data is presented in Fig. S1 (see supplementary material associated with this article online). Of the 2333 subjects who completed the follow-up, 145 participants with prevalent diabetes at

baseline were excluded. Information on diabetes status and HbA1c measurements were not recorded for a further 124 participants, and data on mean PPD and edentulism at baseline were not available for 18 individuals. In addition, 12 subjects were missing covariate information, leaving 2034 participants for the final analyses. For analyses of HbA1c changes from baseline, the relevant sample comprised 1932 subjects after exclusion of 102 patients taking antidiabetic medication.

Periodontitis assessment

Licensed calibrated dentists (eight in SHIP-0, six in SHIP-2) performed the oral examinations. The periodontal recording protocols in SHIP-0 and SHIP-2 were identical. Periodontal measurements were assessed at four sites (distobuccal, mesiobuccal, midbuccal, midlingual/midpalatinal) per tooth according to the half-mouth method, alternating on the left or right side and excluding third molars. A periodontal probe (PCP11, Hu-Friedy Mfg. Co., LLC, Chicago, IL, USA) was used to assess PPD and CAL. PPD was measured as the distance between the free gingival margin and pocket base, while CAL was the distance between the cementoenamel junction (CEJ) and pocket base. If the CEJ was visible, then CAL and PPD were measured directly; otherwise, the distance between the gingival margin and CEJ was subtracted from the PPD to calculate the CAL. Where the CEJ was indistinct (due to, for example, wedge-shaped defects, fillings, crown margins), CAL was not recorded. Measurements were mathematically rounded to the nearest mm. The number of teeth present was counted, excluding third molars.

Calibration exercises were performed during the course of both studies. Dentists were trained *a priori* by the same periodontist (T.K.). For CAL, interclass correlations were 0.84 in SHIP-0 and

0.74 in SHIP-2, whereas intraclass correlations per examiner were 0.82–0.91 in SHIP-0 and 0.76–0.88 in SHIP-2 [25, 26].

To assess periodontitis status, PPD was defined as the primary measure. The mean PPD [19], percentage of sites with PPD ≥ 3 mm [18, 19] and cumulative PPD [sum of the deepest PPDs (≥ 4 mm) per tooth] [20] were calculated on the individual level and categorized as either Q1–Q4 or analyzed continuously. CAL was defined as the secondary exposure measure. The mean CAL and percentage of sites with CAL ≥ 3 mm [18, 19] were calculated on the subject level and categorized as either Q1–Q4 or analyzed continuously. If PPD and CAL definitions were analyzed as Q1–Q4, then edentulous subjects were considered an additional category. If PPD and CAL definitions were analyzed continuously, then edentulous subjects were excluded. Self-reported gum treatment between SHIP-0 (baseline) and SHIP-2 was assessed.

Diabetes definition

At each examination (SHIP-0, SHIP-1, SHIP-2), known diabetes was defined as previously diagnosed cases according to self-reported physician diagnoses or treatment with antidiabetic medication [Anatomical Therapeutic Chemical (ATC) classification system codes A10A and A10B]. At baseline, diabetes was defined as known diabetes in SHIP-0, or as HbA1c levels ≥ 6.5% [27] or non-fasting blood glucose levels ≥ 11.1 mmol/L (both measured in SHIP-0) [28]. For SHIP-2, diabetes was defined as known diabetes in SHIP-2 or HbA1c levels ≥ 6.5% or non-fasting blood glucose levels ≥ 11.1 mmol/L (both measured in SHIP-2). Incident diabetes was the primary outcome, defined as new diabetes cases identified during the entire follow-up period, whereas prevalent cases were excluded from the analyses. HbA1c change was considered a

secondary outcome (SHIP-2 HbA1c – baseline HbA1c) and, in these HbA1c analyses, subjects taking antidiabetic medications during either SHIP-1 or SHIP-2 were excluded.

Laboratory measurements

Samples for measuring non-fasting blood glucose were taken from the cubital vein with subjects in a supine position. HbA1c was measured by high-performance liquid chromatography (Diamat Analyzer System, Bio-Rad Laboratories, Hercules, CA, USA), and non-fasting glucose concentrations by a Hitachi 717 analyzer (Roche Diagnostics, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured with the Hitachi 704 analyzer (Roche Diagnostics), and high-sensitivity C-reactive protein (hs-CRP) was determined immunologically on a Behring Nephelometer II analyzer (Dade Behring, Eschborn, Germany).

Covariate assessments

Sociodemographic and behavioural risk factors were assessed by computer-assisted interviews. Socioeconomic status was assessed as the highest level of general (secondary) education (categorized as < 10, 10 or > 10 years), with marital status categorized as single and living alone, living together, divorced or still married but living alone, or widowed and living alone. To assess cigarette-smoking behaviours, information on smoking status (never, former, current) was combined with number of pack-years (cigarettes/day for X years of smoking/20). Participants were considered physically active if they did ≥ 1 h of physical exercise per week during summer or winter. Self-reported dental visits in the past 12 months were categorized as no or yes. Waist circumference was measured according to WHO standards, using a measuring tape horizontally

midway between the lowermost rib margin and iliac crest (to the nearest 0.1 cm). Lipid-lowering medication was defined as ATC codes C10AA and/or C10AB, and antihypertensive medication was defined as ATC codes C02A, C03C, C03E, C08DA, C09BA, C07A, C08C, C09AA and/or C09CA.

After a resting period of at least 5 min, systolic (SBP) and diastolic blood pressure (DBP) was measured three times on the right arm of seated subjects, using an oscillometric digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). The time interval between the three readings was 3 min. The mean of only the second and third measurements was calculated, and hypertension was defined as self-reported use of antihypertensive medication, or SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg.

Statistical analyses

Directed acyclic graphs (DAGs) were constructed to minimize bias in the selected confounders. DAGs are used to explore the causal structure thought to underlie the exposure/outcome association of interest [29]. Moreover, they represent a new graphic analytical tool for determining adjustment sets [30]. DAGitty software [31] was used for DAG creation and determination of minimal sufficient adjustment sets. The final DAG is presented in Fig. S2 (see supplementary material associated with this article online). Accordingly, the minimal sufficient adjustment set included age, gender, social determinants (assessed by the highest level of general education and marital status), smoking status, central adiposity (assessed by waist circumference), physical activity and general health behaviour (assessed by self-reported dental visits in the past 12 months). To reduce the potential of confounding when estimating the exposure/outcome association of interest, factors identified for the minimal sufficient adjustment

sets were included as independent variables in regression models (referred to as adjustments). To assess the magnitude of confounding by single factors, crude, age- and gender-adjusted, and fully adjusted models were also presented.

Means ± standard deviations (SDs), medians (Q25%–Q75%) or numbers (%) were reported as appropriate. Chi-square and Mann–Whitney U tests were used to assess distributional differences between unpaired groups. Paired *t*, McNemar and Wilcoxon signed-rank tests were applied to test for distributional differences between paired groups.

Modified Poisson regression models with robust standard errors were used to estimate risk of diabetes in association with periodontal parameters. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were reported. In addition, multivariable linear regression models assessed the effects of baseline periodontitis on long-term HbA1c changes, along with β coefficients and 95% CIs. Models were adjusted for age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status and dental visits in the last 12 months. Logarithmic follow-up time was considered an offset variable. To retrieve *P* values for linear trends, categorical variables were treated in regression models as if they were continuous. To account for selection bias introduced by complete case analyses [32], all analyses were weighted using inverse probability weighting (IPW). Logistic models for generating IPWs included age, gender, highest level of general education, marital status, smoking status, physical activity, waist circumference, hypertension and number of missing teeth.

All analyses were conducted with Stata/SE 14.1 software (StataCorp, College Station, TX, USA) [33]. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Analyses for incident diabetes

During a mean follow-up period of 11.1 years, 206 incident diabetes cases were identified (Table I). On average, these cases were 9 years older, and exhibited a poorer periodontal status (Table I) and a deteriorated metabolic status (Table S1; see supplementary material associated with this article online) compared with non-incident subjects.

In crude models, incidence rates increased significantly across all categories of periodontal definitions ($P_{trend} < 0.001$, Table II). For CAL-based definitions, associations diminished after inclusion of age and gender, indicating minor confounding by the remaining factors. For PPD-based definitions, associations diminished after inclusion of age, gender and central adiposity. Thus, in the fully adjusted models, no consistently statistically significant effects were observed for any of the exposure definitions. Only one significant finding was found when edentulous subjects were compared with those with the lowest mean PPD (IRR: 1.973, 95% CI: 1.075–3.620). Non-significant results were found for quartiles of mean PPD (IRR: 1.271, 95% CI: 0.782–2.065, Q4 *vs* Q1) and for quartiles of mean CAL (IRR: 0.819, 95% CI: 0.489–1.370). Moreover, there was no apparent overall trend to indicate increasing IRRs across exposure categories ($P_{trend} > 0.05$). Whether using continuous definitions of exposure by mean PPD and mean CAL (Table II) or alternative periodontitis definitions, such as the cumulative PPD, percentage of sites with PPD ≥ 3 mm or percentage of sites with CAL ≥ 3 mm (Table S2; see supplementary material associated with this article online), the results were consistent.

Analyses for HbA1c changes

Although crude changes in HbA1c levels differed across quartiles of periodontal definitions, with the highest levels found for edentulate subjects, periodontal definitions were not associated with HbA1c changes in fully adjusted analyses (Table III). Exchanging quartile definitions for continuous definitions of mean PPD or mean CAL, or for alternative periodontitis measures such as cumulative PPD, percentage of sites with PPD ≥ 3 mm or percentage of sites with CAL ≥ 3 mm (Table S3; see supplementary material associated with this article online) led to consistent results.

DISCUSSION

The present longitudinal study found no evidence of an association between periodontitis and incidence of diabetes after full adjustment for confounders. Moreover, our findings did not support the hypothesis that baseline periodontitis may affect HbA1c levels over an average period of 11.1 years. Specifically, associations for CAL-based exposure definitions became non-significant after adjustments for age and gender, indicating minor confounding by the remaining factors. For PPD-based exposure definitions, additional adjustment for central adiposity rendered the associations non-significant. Thus, our results are not in line with the previous studies that reported an association of periodontitis with incident diabetes or HbA1c changes [11–13, 15].

To explain the lack of association in the present study, the following arguments may be considered. The first is survivor bias, meaning that those subjects with periodontitis who were more susceptible to diabetes were less likely to complete the follow-up than those with periodontitis who were less susceptible to diabetes, and this may have substantially affected the composition of the study population by giving rise to a healthier cohort that was not representative of the target population. Also, in general, as excluded subjects might differ

systematically in their disease profiles from study participants, our effect estimates may have been underestimated [34]. To reduce biases, analyses were weighted using IPWs, which largely removed selection bias. Second, periodontitis can cause low-grade systemic inflammation, thereby affecting progression of insulin resistance [6, 35]. However, no inflammatory progression was observed in our incident diabetes and/or prediabetes participants during the follow-up (data not shown). In a previous study, a moderate effect of periodontitis on systemic inflammation was observed in lean participants, but not in the abdominally obese [36]. The reason for such a lack of inflammatory progression might be that participants with incident diabetes and/or prediabetes were already on the brink of central adiposity at baseline. Thus, progression of inflammation might not have been enough to promote periodontal effects in diabetes.

To date, only limited epidemiological data are available to answer the question of whether severe periodontal infections contribute to decreased insulin sensitivity or the development of diabetes in diabetes-free individuals. The results of one cross-sectional [13] and three longitudinal studies [11, 12, 37] are contrary to those of the present study. The reasons for these discrepancies are currently unknown, but might be related to methodological factors.

In the first population-based longitudinal study of this topic and using data from the first NHANES (1971–1976), a non-linear positive association between baseline periodontal disease category (defined by quartiles of the percentage of sites with CAL $\geq$ 5 mm) and incident T2D was reported, claiming elevated odds ratios across increasing periodontal disease categories [13]. To assess periodontitis, those authors used Russell's Periodontal Index (RPI), a composite index of gingivitis and periodontitis that did not capture the exact severity or extent of probing depth or attachment levels. Today, with our better understanding of periodontal disease, the RPI is no

longer used because of concerns regarding its validity, underlying assumptions, and poor discrimination between moderate and severe periodontitis [38]. Thus, the severity of periodontitis might have been overestimated by Demmer et al. [13]. In addition, there were no available HbA1c or fasting glucose data to exclude undiagnosed diabetes at baseline, making results susceptible to a misclassification bias. In a Taiwanese nationwide retrospective study, patients (aged ≥ 40 years) with severe periodontitis (as indicated by subsequent periodontal surgery) had an increased risk (HR: 1.19, 95% CI: 1.10–1.29) of future diabetes compared with periodontitis patients not undergoing surgery [11]. However, this study is not considered reliable because of the uncertainty of the appropriateness of the statistical analyses for the study design and inadequate characterization of the two patient groups. In addition, statistical models were not adjusted for smoking and central adiposity, factors suggested to be common risk factors for periodontitis and diabetes [39, 40]. In particular, central adiposity proved to be a major confounder in our analyses. When central adiposity was included in regression models, associations became non-significant. Thus, residual confounding might be a serious drawback of this Taiwanese study.

More recently, a 5-year follow-up study of male Japanese workers aged 36–55 years [12] observed a similar relationship between the presence of loose teeth and incident diabetes, and reported a higher risk after adjusting for confounders (RR: 1.73, 95% CI: 1.14–2.64) in those with tooth-loosening. However, periodontitis was only assessed by a self-administered questionnaire that included questions about gingival haemorrhage or tooth-loosening at baseline, with no clinical assessment. Furthermore, measurements of HbA1c to detect cases of prediabetes at baseline were not fully available during the study. As a consequence, diabetes patients were probably not definitively identified, which may have introduced a misclassification bias and,

thus, a shift of risk estimates to a null effect. In contrast to previous studies but in accordance with our present one, a large prospective study [14] comprising 5848 diabetes-free Japanese subjects aged 30–59 years found a non-significant association (HR: 1.28, 95% CI: 0.89–1.86) between severe periodontitis and diabetes incidence. Thus far, the current literature has provided no concrete evidence of a causal association between periodontitis and diabetes incidence, with the methodological quality of the available studies being a major issue. Finally, direct comparisons between studies may not be deemed appropriate because of other, variable factors, such as the characteristics of the study population and use of different diagnostic criteria for exposure/outcome.

The present study was well designed, and clearly delineates the temporality of exposure and outcome. The SHIP is a large-scale population-based study covering a wide age range (20–81 years). Also, exposure was comprehensively assessed using clinical measurements to define severity (mean PPD, mean CAL) and extent of periodontitis (percentage of sites with PPD $\geq$ 3 mm, percentage of sites with CAL $\geq$ 3 mm), and also the cumulative inflammatory burden (cumulative PPD). Furthermore, edentulism as a long-term consequence of untreated severe periodontitis was analyzed. The fact that all of the various exposure definitions led to the same results strengthens the finding that periodontitis was not associated with either incident diabetes or HbA1c changes in the present study.

The presence of diabetes was ascertained by physician diagnoses, use of antidiabetic medications, and HbA1c and non-fasting plasma glucose measurements to minimize misclassification bias. In addition, two outcome definitions were employed. The diabetes definition provides easily interpretable IRRs as effects estimates and also includes participants taking antidiabetic medications, making it the better outcome definition for our study. For the

HbA1c analyses, subjects taking newly prescribed antidiabetic medications were excluded to prevent attenuation of HbA1c changes and, in turn, attenuation of effects estimates. Using both outcome definitions led to similar findings, thereby strengthening the credibility of our findings. Furthermore, the long prospective follow-up and comprehensive adjustment of confounders increases the relevance of our study as evidence concerning the periodontitis–diabetes relationship.

However, at least six limitations of the present study merit consideration. First, because the study sample solely comprised Caucasians from northeast Germany, our findings cannot be generalized to other ethnicities. Second, as full-mouth examinations with six sites per tooth (the gold standard) would have been too time-consuming and cost-intensive, the SHIP used a half-mouth protocol with only four sites, which might have led to underestimation of periodontal disease severity [41, 42], with dilution of effects estimates towards null, assuming that misclassification occurred non-differentially [43]. Third, although DAGs informed by clinical and epidemiological knowledge were used to determine our adjustment sets, it is not possible to entirely exclude the possibility of residual confounding by, for instance, diet, genetic factors or other, unknown factors not considered in the DAG. Fourth, HbA1c change was assessed using measurements at two time points, thereby reflecting glycaemic variability to only a limited extent. However, analyses of HbA1c change considering three time points (SHIP-0/-1/-2) were not possible. Fifth, because the periodontal probe used in SHIP-1 was different from those of SHIP-0 and SHIP-2 [44], their periodontal measurements are not comparable. Finally, 21% of subjects (n = 1985 due to missing information) reported having some form of ‘gum treatment’ between baseline and the end of the 11-year follow-up. However, no details of the type and duration of such treatment were available. Also, as patients may not have a clear understanding

of what the standard periodontal treatment is [45], such self-reported 'gum treatment' should perhaps be interpreted with caution. Thus, the percentage of subjects receiving regular periodontal therapy during follow-up can be assumed to be much lower, with negligible effects on HbA1c change and its association with periodontitis.

CONCLUSION

Periodontitis was not associated with incident diabetes after making DAG-guided comprehensive adjustments to the prospective 11-year follow-up data from the SHIP. Thus, our findings do not support the hypothesis that baseline or periodontitis progression may have an effect on HbA1c changes. Large prospective cohort studies of diverse populations, which will minimize bias at both design and analytical stages, are necessary to further scrutinize the evidence for this relationship.

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Appendix supplementary material

Supplementary materials (Figs. S1–S2, Tables S1–S3) associated with this article can be found at http://www.scincedirect.com at doi . . .

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Supplemetary figure legends

Fig. S1. Flow chart of the study analysis set showing reasons for non-response in the second Study of Health in Pomerania (SHIP-2), as well as the exclusion criteria, and number and type of missing data.

Fig. S2. The main directed acyclic graph (DAG) created to evaluate the association between periodontitis and diabetes.

Table I. Baseline characteristics of Study of Health in Pomerania (SHIP-0) participants by incident diabetes over the 11-year follow-up

	Diabetes prevalence (n = 145)	**Analyses of incident diabetes**		**Analyses of HbA1c change**
		Non-incident (n = 1828)	**Incident (n = 206)**	**Total sample (n = 1932)**
Age, years	56.8 ± 10.3	45.0 ± 13.4	53.7 ± 11.8#	45.4 ± 13.5
Gender:				
Female	57 (39.3)	989 (54.1)	96 (46.6)	1043 (54.0)
Male	88 (60.7)	839 (45.9)	110 (53.4)#	889 (46.0)
Highest level of general education:				
< 10 years	82 (56.6)	439 (24.0)	86 (41.8)	482 (24.9)
10 years	41 (28.3)	1005 (55.0)	92 (44.7)	1049 (54.3)
> 10 years	22 (15.2)	384 (21.0)	28 (13.5)#	401 (20.8)
Marital status:				
Single, living alone	6 (4.1)	198 (10.8)	13 (6.3)	203 (10.5)
Living together	121 (83.5)	1476 (80.7)	160 (77.7)	1553 (80.4)
Divorced or still married, but living alone	8 (5.5)	95 (5.2)	22 (10.7)	109 (5.6)
Widowed, living alone	10 (6.9)	59 (3.2)	11 (5.3)#	67 (3.5)
Smoking status:				
Never smoker	49 (33.8)	736 (40.3)	76 (36.9)	774 (40.1)
Former smoker, < 20 pack years	49 (33.8)	509 (27.8)	57 (27.7)	540 (28.0)
Former smoker, ≥ 20 pack years	19 (13.1)	93 (5.1)	21 (10.2)	101 (5.2)
Current smoker, < 20 pack years	10 (6.9)	359 (19.6)	23 (11.2)	372 (19.2)
Current smoker, ≥ 20 pack years	18 (12.4)	131 (7.2)	29 (14.1)#	147 (7.5)
Physical activity, yes	39 (26.9)	897 (49.1)	80 (38.8)#	937 (48.5)
Waist circumference, cm	100.0 ± 12.9	85.7 ± 12.7	98.1 ± 12.0#	86.2 ± 12.8

HbA1c, %	7.2 ± 1.5	5.1 ± 0.5	5.7 ± 0.5#	5.2 ± 0.5
Edentulous, yes	21 (14.5)	65 (3.5)	26 (12.6)#	75 (3.9)
Number of missing teeth	10 (5–22)	4 (2–9)	8 (3–19)#	5 (2–10)
Mean PPD, mm*	2.77 ± 0.82	2.40 ± 0.65	2.63 ± 0.75#	2.41 ± 0.64
Mean CAL, mm†	3.39 ± 1.71	2.27 ± 1.60	2.94 ± 1.62#	2.29 ± 1.60

Data are means ± SD or medians (Q25%–Q75% for number of missing teeth) or numbers (%); * n = 123 subjects with prevalent diabetes; † n = 114/1887/1805 for subjects with prevalent diabetes/in incident diabetes analysis set/in HbA1c change analysis set; # $P < 0.05$ for incident *vs* non-incident subjects, calculated by Mann–Whitney U (continuous variables) or chi-square (categorical variables) tests;
HbA1c: haemoglobin A1c; PPD: pocket probing depth; CAL: clinical attachment level

Table II. Results of modified Poisson models regressing incident diabetes on baseline periodontal status

	Incidence rate (per 1000 person-years)	**Crude IRR (95% CI)**	**Age-/gender-adjusted IRR (95% CI)**	**Fully adjusted IRR (95% CI)**	***P***
Mean pocket probing depth, mm					
Analyzed as quartiles (Q; n = 2034)					
Q1 (0.95–1.97)	4.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Q2 (1.98–2.30)	8.7	2.185 (1.325–3.603)*	1.873 (1.136–3.087)*	1.352 (0.819–2.232)	0.239
Q3 (2.31–2.69)	8.8	2.304 (1.397–3.802)*	1.733 (1.047–2.868)*	1.224 (0.749–1.999)	0.420
Q4 (2.70–7.25)	11.6	2.842 (1.759–4.593)*	1.925 (1.173–3.158)*	1.271 (0.782–2.065)	0.333
Edentulous	25.8	5.989 (3.489–10.280)*	2.858 (1.587–5.146)*	1.973 (1.075–3.620)	0.028
		$P_{trend} < 0.001$	$P_{trend} = 0.003$	$P_{trend} = 0.110$	
Analyzed continuously (n = 1943)	–	1.397 (1.207–1.618)*	1.231 (1.030–1.471)*	1.061 (0.876–1.286)	0.545
Mean clinical attachment level, mm					
Analyzed as Q (n = 1978)					
Q1 (0–1.15)	4.7	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Q2 (1.16–2.04)	4.6	0.955 (0.545–1.674)	0.740 (0.421–1.302)	0.610 (0.357–1.040)	0.069
Q3 (2.05–3.14)	9.4	1.940 (1.201–3.135)*	1.162 (0.679–1.989)	0.915 (0.563–1.489)	0.722
Q4 (3.15–12.25)	13.9	2.853 (1.809–4.501)*	1.382 (0.765–2.495)	0.819 (0.489–1.370)	0.446
Edentulous	25.8	5.186 (3.068–8.769)*	2.029 (1.008–4.082)*	1.300 (0.666–2.539)	0.442
		$P_{trend} < 0.001$	$P_{trend} = 0.011$	$P_{trend} = 0.30$	
Analyzed	–	1.173 (1.102–	1.024 (0.929–	0.929 (0.836–	0.177

continuously (n = 1887)		1.249)*	1.127)	1.034)	

Fully adjusted models included age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status (5 categories, including pack-years), dental visits in past 12 months, follow-up time (ln, offset); all models were weighted using inverse probability weighting;
* $P < 0.05$;
IRR: incidence rate ratio; CI: confidence interval

Table III. Results of linear regression models evaluating associations between baseline periodontal status and 11-year changes in haemoglobin A1c (HbA1c, %) in subjects not taking antidiabetic medications

	Changes in HbA1c, %	**Crude β (95% CI)**	**Age-/gender-adjusted β (95% CI)**	**Fully adjusted β (95% CI)**	***P***
Mean pocket probing depth, mm					
Analyzed as quartiles (Q, n = 1932)					
Q1 (0.95–1.97)	0.13 ± 0.58	0.00 (reference)	0.00 (reference)	0.00 (reference)	
Q2 (1.98–2.30)	0.22 ± 0.76	0.082 (-0.006–0.170)	0.067 (-0.022–0.156)	0.062 (-0.027–0.151)	0.172
Q3 (2.31–2.68)	0.18 ± 0.56	0.060 (-0.020–0.140)	0.026 (-0.058–0.111)	0.003 (-0.081–0.087)	0.939
Q4 (2.69–7.25)	0.25 ± 0.67	0.123 (0.041–0.206)*	0.074 (-0.015–0.164)	0.038 (-0.053–0.129)	0.414
Edentulous	0.23 ± 0.54	0.126 (-0.026–0.278)	0.042 (-0.119–0.203)	0.009 (-0.156–0.174)	0.915
		$P_{trend} = 0.013$	$P_{trend} = 0.321$	$P_{trend} = 0.848$	
Analyzed continuously (n = 1857)	0.19 ± 0.65	0.046 (0.001–0.091)*	0.025 (-0.022–0.072)	0.003 (-0.045–0.051)	0.914
Mean clinical attachment level, mm					
Analyzed as Q (n = 1880					
Q1 (0–1.12)	0.18 ± 0.73	0.00 (reference)	0.00 (reference)	0.00 (reference)	
Q2 (1.13–2.01)	0.20 ± 0.56	0.042 (-0.040–0.124)	0.009 (-0.074–0.091)	-0.010 (-0.091–0.072)	0.820
Q3 (2.02–3.09)	0.17 ± 0.58	0.041 (-0.046–0.127)	-0.028 (-0.116–0.060)	-0.062 (-0.152–0.027)	0.173
Q4 (3.10–12.25)	0.22 ± 0.69	0.084 (-0.004–0.173)	-0.019 (-0.125–0.086)	-0.086 (-0.187–0.016)	0.098
Edentulous	0.23 ± 0.54	0.104 (-0.049–0.257)	-0.029 (-0.195–0.137)	-0.096 (-0.263–0.072)	0.262
		$P_{trend} = 0.054$	$P_{trend} = 0.584$	$P_{trend} = 0.071$	
Analyzed continuously (n = 1805)	0.19 ± 0.64	0.018 (-0.005–0.041)	0.001 (-0.029–0.031)	-0.013 (-0.042–0.015)	0.364

Changes in HbA1c are means ± SD; models were adjusted for age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status (5 categories, including pack-years), dental visits in past 12 months, follow-up time (ln, offset), and weighted using inverse probability weighting;
β: linear regression coefficient; CI: confidence interval

Table S1. Additional clinical baseline data used for analyses of incident diabetes and changes in haemoglobin A1c (HbA1c) from baseline

	Analyses of incident diabetes				Analyses of HbA1c change	
		Incident diabetes				
	n (non-incident/incident)	No	Yes	*P*	n	Total sample
Serum glucose, mmol/L	1808/198	5.21 ± 0.70	5.93 ± 1.13	0.0001	1908	5.23 ± 0.72
HDL-C, mmol/L	1808/198	1.51 ± 0.42	1.28 ± 0.36	0.0001	1908	1.51 ± 0.42
LDL-C, mmol/L	1808/198	3.51 ± 1.14	3.87 ± 1.28	0.0001	1908	3.52 ± 1.15
Lipid medication*	1808/198				1908	
No		1731 (95.7)	176 (88.9)			1820 (95.4)
Yes		77 (4.3)	22 (11.1)	< 0.0001		88 (4.6)
Antihypertensive medication#	1808/198				1908	
No		1526 (84.4)	119 (60.1)			1595 (83.6)
Yes		282 (15.6)	79 (39.9)	< 0.0001		313 (16.4)
Hypertension†	1808/198				1908	
No		1053 (58.2)	60 (30.3)			1096 (57.4)
Yes		755 (41.8)	138 (69.7)	< 0.0001		812 (42.6)
hs-CRP, mg/L	1646/181	1.92 ± 2.21	2.98 ± 2.76	0.0001	1739	1.98 ± 2.28
≤ 2 mg/L	1760/193	1220 (69.3)	99 (51.3)		1739	1216 (69.9)
> 2 mg/L but ≤ 3 mg/L		194 (11.0)	16 (8.3)			179 (10.3)
> 3 mg/L		346 (19.7)	78 (40.4)	< 0.0001		344 (19.8)

Data are means ± SD or numbers (%); *P* values were calculated by Mann–Whitney U (continuous variables) and chi-square (categorical variables) tests; * ATC codes C10AA, C10AB; # ATC codes C02A, CO3C, C03E, C08DA, C09BA, C07A, C08C, C09AA, C09CA; † use of antihypertensive medications, or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg;
HDL-C/LDL-C: high-density lipoprotein/low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein

Table S2. Results of modified Poisson models regressing incident diabetes on baseline periodontal status

	Incidence rate (per 1000 person-years)	Crude IRR (95% CI)	Age-/gender-adjusted IRR (95% CI)	Fully adjusted IRR (95% CI)	*P*
Percentage of sites with PPD ≥ 3 mm					
Analyzed as quartiles (Q, n = 2034)					
Q1 (0–25.4)	5.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Q2 (25.5–41.7)	9.0	1.658 (1.055–2.605)*	1.551 (0.995–2.418)	1.423 (0.908–2.232)	0.124
Q3 (41.8–59.5)	6.7	1.215 (0.754–1.957)	0.987 (0.611–1.594)	0.823 (0.509–1.329)	0.425
Q4 (59.6–100)	12.5	2.325 (1.523–3.549)*	1.711 (1.113–2.631)*	1.253 (0.808–1.943)	0.313
Edentulous	25.8	4.424 (2.698–7.255)	2.228 (1.307–3.798)*	1.783 (1.014–3.137)	0.045
		$P_{trend} < 0.001$	$P_{trend} = 0.004$	$P_{trend} = 0.139$	
Analyzed continuously, per 10% increase (n = 1943)	–	1.012 (1.007–1.018)*	1.008 (1.001–1.014)*	1.009 (0.948–1.073)	0.786
Cumulative PPD					
Analyzed as Q (n = 2034)					
Q1 (0–3)	5.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Q2 (4–8)	7.7	1.143 (0.733–1.782)	1.024 (0.657–1.596)	0.986 (0.635–1.531)	0.951
Q3 (9–18)	10.2	1.551 (0.999–2.407)	1.196 (0.768–1.862)	1.086 (0.710–1.661)	0.705
Q4 (19–97)	10.5	1.666 (1.102–2.519)*	1.374 (0.910–2.075)	1.125 (0.751–1.684)	0.568
Edentulous	25.8	3.693 (2.293–5.948)*	1.884 (1.117–3.177)*	1.670 (0.983–2.837)	0.058
		$P_{trend} < 0.001$	$P_{trend} = 0.008$	$P_{trend} = 0.077$	
Analyzed continuously per 10% increase (n = 1943)	–	1.115 (1.027–1.211)*	1.090 (0.997–1.191)	1.026 (0.938–1.121)	0.579
Percentage of sites with CAL ≥ 3 mm					
Analyzed as Q (n = 1978)					
Q1 (0–10.8)	3.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Q2 (10.9–35.8)	6.0	1.545 (0.885–2.699)	1.132 (0.646–1.985)	0.859 (0.499–1.480)	0.585
Q3 (35.9–70.3)	9.4	2.427 (1.453–4.051)*	1.403 (0.812–2.423)	0.997 (0.591–1.680)	0.990
Q4 (70.4–100)	13.3	3.334 (2.038–5.455)*	1.588 (0.870–2.897)	0.917 (0.527–1.596)	0.758
Edentulous	25.8	6.349 (3.646–11.056)*	2.400 (1.193–4.831)*	1.468 (0.726–2.967)	0.285
		$P_{trend} < 0.001$	$P_{trend} = 0.010$	$P_{trend} = 0.298$	
Analyzed continuously, per	–	1.134 (1.086–	1.050 (0.990–	0.983 (0.932–	0.532

10% increase (n = 1887)	1.183) *	1.114)	1.037)

Models adjusted for age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status (5 categories, including pack-years), dental visits in last 12 months, follow-up time (ln, offset), and weighted using inverse probability weighting; * *P* < 0.05;

IRR: incidence rate ratio; CI: confidence interval; PPD: pocket probing depth; CAL: clinical attachment level

Table S3. Results of linear regression models evaluating associations between baseline periodontal status (additional periodontitis definitions) and 11-year changes in haemoglobin A1c (HbA1c) in subjects not taking antidiabetic medications

	Changes in HbA1c, %	**Crude β (95% CI)**	**Age-/gender-adjusted β (95% CI)**	**Fully adjusted β (95% CI)**	***P***
	Percentage of sites with PPD ≥ 3 mm, %				
Analyzed as quartiles (Q, n = 1932)					
Q1 (0–25.4)	0.14 ± 0.55	0.00 (reference)	0.00 (reference)	0.00 (reference)	
Q2 (25.5–41.7)	0.22 ± 0.80	0.084 (-0.006–0.173)	0.076 (-0.013–0.165)	0.062 (-0.028–0.151)	0.177
Q3 (41.8–58.7)	0.17 ± 0.54	0.029 (-0.046–0.103)	0.0004 (-0.077–0.077)	-0.019 (-0.098–0.061)	0.644
Q4 (58.8–100)	0.25 ± 0.68	0.130 (0.049–0.211)	0.090 (0.007–0.174)*	0.047 (-0.042–0.136)	0.297
Edentulous	0.23 ± 0.54	0.118 (-0.032–0.269)	0.039 (-0.116–0.194)	0.005 (-0.153–0.164)	0.947
		P_{trend} = 0.011	P_{trend} = 0.211	P_{trend} = 0.734	
Analyzed continuously, per 10% increase (n = 1857)	0.19 ± 0.65	0.020 (0.007–0.033)*	0.015 (0.001–0.028)*	0.008 (-0.007–0.023)	0.298
	Cumulative PPD, mm				
Analyzed as Q (n = 1932)					
Q1 (0–3)	0.15 ± 0.55	0.00 (reference)	0.00 (reference)	0.00 (reference)	
Q2 (4–8)	0.21 ± 0.78	0.081 (-0.006–0.167)	0.065 (-0.022–0.152)	0.043 (-0.042–0.128)	0.322
Q3 (9–18)	0.19 ± 0.57	0.039 (-0.039–0.117)	0.002 (-0.079–0.083)	-0.022 (-0.103–0.059)	0.597
Q4 (19–97)	0.23 ± 0.66	0.085 (0.008–0.162)*	0.055 (-0.025–0.134)	0.026 (-0.053–0.105)	0.520
Edentulous	0.23 ± 0.54	0.105 (-0.044–0.255)	0.023 (-0.133–0.178)	-0.008 (-0.164–0.149)	0.924
		P_{trend} = 0.068	P_{trend} = 0.541	P_{trend} = 0.993	
Analyzed continuously, per 10% increase (n = 1857)	0.19 ± 0.65	0.018 (-0.005–0.041)	0.013 (-0.011–0.036)	0.007 (-0.016–0.030)	0.544
	Percentage of sites with CAL ≥ 3 mm, %				
Analyzed as Q (n = 1880)					
Q1 (0–10.5)	0.17 ± 0.71	0.00 (reference)	0.00 (reference)	0.00 (reference)	
Q2 (10.6–35.0)	0.19 ± 0.57	0.040 (-0.041–0.122)	0.005 (-0.078–0.088)	-0.007 (-0.089–0.074)	0.858
Q3 (35.1–69.3)	0.17 ± 0.58	0.039 (-0.046–0.124)	-0.025 (-0.113–0.064)	-0.053 (-0.141–0.034)	0.233
Q4 (69.4–100)	0.24 ± 0.69	0.105 (0.018–0.193)*	0.014 (-0.089–0.118)	-0.050 (-0.150–0.049)	0.319
Edentulous	0.23 ± 0.54	0.109 (-0.043–	-0.009 (-	-0.070 (-	0.407

		0.262) $P_{trend} = 0.021$	0.174–0.157) $P_{trend} = 0.950$	0.236–0.096) $P_{trend} = 0.225$	
Analyzed continuously, per 10% increase (n = 1805)	0.19 ± 0.64	0.011 (0.001–0.021)*	0.003 (-0.010–0.015)	-0.005 (-0.017–0.007)	0.411

Data are means ± SD unless otherwise indicated; models were adjusted for age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status (5 categories, including pack-years), dental visits in last 12 months, follow-up time (ln, offset), and weighted using inverse probability weighting; * $P < 0.05$;

PPD: pocket probing depth; CAL: clinical attachment level

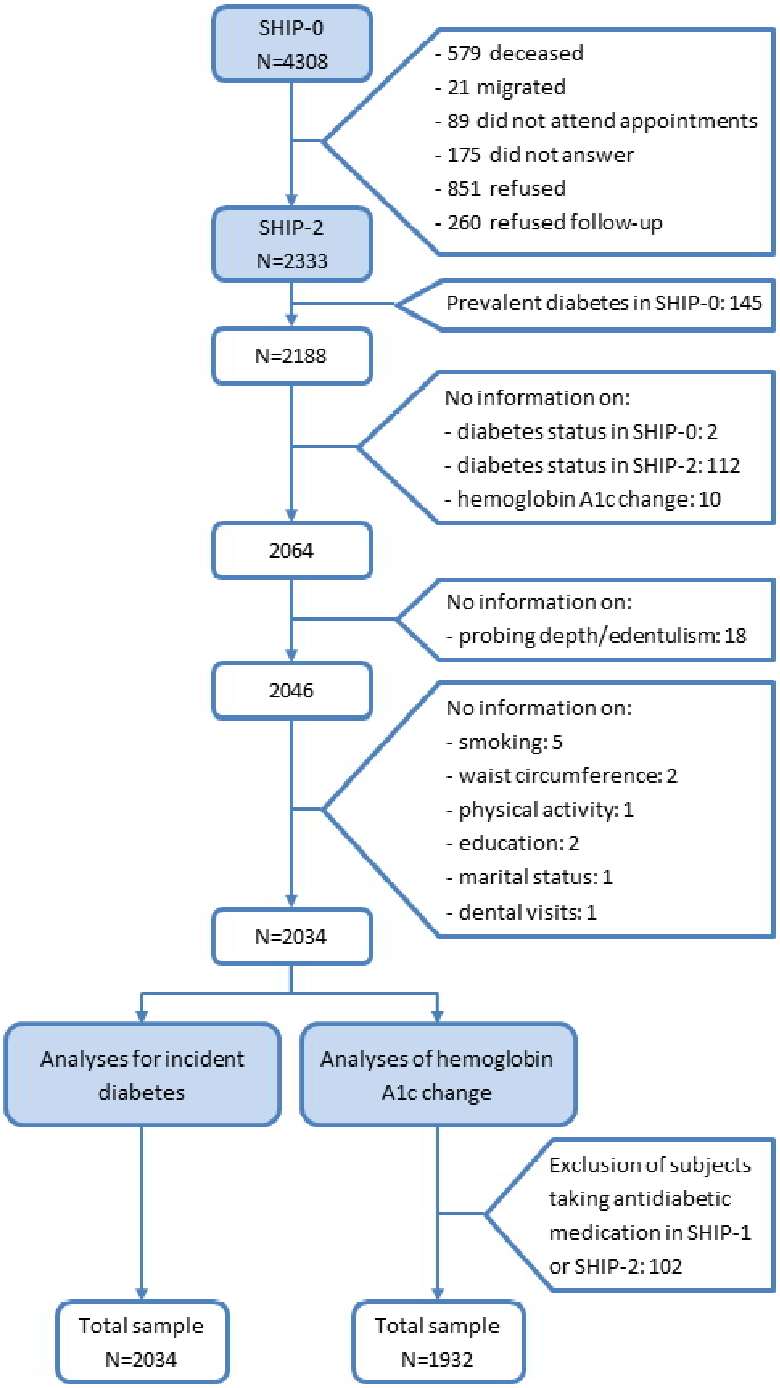

Fig. S1. Flow chart of the analysis set, showing reasons for nonresponse in SHIP-2 and exclusion criteria and number and type of missing data.

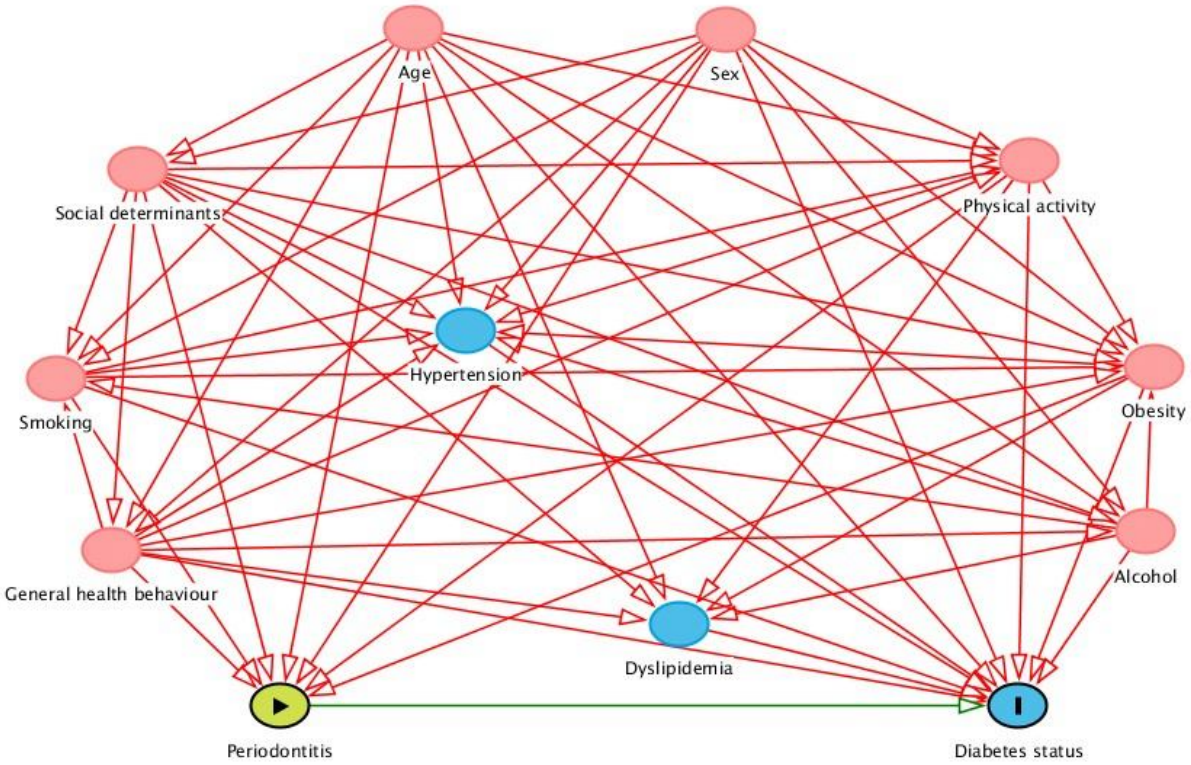

Fig. S2. The main directed acyclic graph (DAG) to evaluate the association between periodontitis and diabetes mellitus.