Different Effects of Lifestyle Intervention in High- and Low-Risk Prediabetes: Results of the Randomized Controlled Prediabetes Lifestyle Intervention Study (PLIS)

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Lifestyle intervention (LI) can prevent type 2 diabetes, but response to LI varies depending on risk subphenotypes. We tested whether individuals with prediabetes with low risk (LR) benefit from conventional LI and individuals with high risk (HR) benefit from an intensification of LI in a multicenter randomized controlled intervention over 12 months with 2 years' follow-up. A total of 1,105 individuals with prediabetes based on American Diabetes Association glucose criteria were stratified into an HR or LR phenotype based on previously described thresholds of insulin secretion, insulin sensitivity, and liver fat content. LR individuals were randomly assigned to conventional LI according to the Diabetes Prevention Program (DPP) protocol or control (1:1) and HR individuals to conventional or intensified LI with doubling of required exercise (1:1). A total of 908 (82%) participants completed the study. In HR individuals, the difference between conventional and intensified LI in postchallenge glucose change was −0.29 mmol/L [95% CI −0.54; −0.04], *P* = 0.025. Liver fat (−1.34 percentage points [95% CI −2.17; −0.50], *P* = 0.002) and cardiovascular risk (−1.82 percentage points [95% CI −3.13; −0.50], *P* = 0.007) underwent larger reductions with intensified than with conventional LI. During a follow-up of 3 years, intensified compared with conventional LI had a higher probability of normalizing glucose tolerance (*P* = 0.008). In conclusion, it is possible in HR individuals with prediabetes to improve glycemic and cardiometabolic outcomes by intensification of LI. Individualized, risk phenotype–based LI may be beneficial for the prevention of diabetes.

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Lifestyle modification is the principal procedure for type 2 diabetes prevention in individuals with prediabetes. During the last two decades, multiple studies have shown that lifestyle intervention (LI) is effective in preventing diabetes. Several prospective randomized studies (1–4) have demonstrated that diabetes risk can be reduced by modifying diet and physical exercise. Such approaches yield relative diabetes risk reductions between 15 and 70% within 1–6 years of follow-up (5). Recent meta-analyses of randomized trials reported mean risk ratios of 0.35 (6), 0.57 (7), and 0.61 (8) in comparisons of LI with usual care. This points to a robust benefit of LI for the prevention of type 2 diabetes, which is sustainable and extends beyond the duration of the intervention (4,9,10).

Nevertheless, there is a pressing need for making LI more efficient for diabetes prevention because a considerable proportion of participants in LI trials do not benefit from the intervention. They are often referred to as "nonresponders" (11,12). For example, every fifth patient of the LI group in the Diabetes Prevention Program (DPP) developed type 2 diabetes within 4 years (2). An alternative definition of nonresponse is the inability to regress from prediabetes to a normal glucose regulation during a LI program (11). In the DPP, only ∼40% of participants accomplished regression to normal glucose regulation (11); i.e., 60% were LI nonresponders. Furthermore, there is the important question of whether LI is necessary in all individuals with prediabetes (13). There are individuals with prediabetes who do not progress to diabetes during 11 years of follow-up even without intervention (14). In such individuals with "intermediate hyperglycemia," LI with the sole purpose of lowering blood glucose might be of less importance. Both observations of nonresponse to LI and nonprogression to diabetes highlight the need for risk stratified intervention strategies in individuals with prediabetes.

The fundamental question is which phenotypes determine the risk for diabetes and especially the response and nonresponse to LI. A recent post hoc analysis of the DPP showed that response varies based on diabetes risk (15), suggesting an adaption of LI on the basis of individual risk.

In a retrospective analysis of the Tübingen Lifestyle Intervention Program (TULIP), we identified a phenotype of high risk (HR) associated with higher probability of short-term (16) and long-term (12) nonresponse to LI. This phenotype represents β-cell dysfunction and/or insulin-resistant nonalcoholic fatty liver disease (NAFLD), which is also associated with increased cardiometabolic risk (17). Similar phenotypes have been identified by cluster analysis in patients with type 2 diabetes or prediabetes (18,19). These approaches show that risk stratification can identify severe disease courses and increased risk for diabetes-related complications both in populations prior to diabetes onset and with diabetes.

Therefore, it is also crucial to improve the efficiency and effectiveness of LI programs in HR participants to overcome nonresponse to preventive interventions. Unnecessary overtreatment can be avoided by identification of individuals at low risk (LR) who do not need treatment. We designed a prospective risk-stratified randomized controlled multicenter LI study. Within the Prediabetes Lifestyle Intervention Study (PLIS), we performed two randomized controlled trials: One was in the HR individuals to answer the question, *1*) can nonresponse in HR individuals with prediabetes be overcome by intensification of LI? And the second was in LR individuals to answer the question, *2*) is LI effective in LR individuals with prediabetes? The primary hypothesis is that individuals with prediabetes who have high risk for a failure to restore normal glucose regulation with conventional LI will benefit from an intensification of the LI.

RESEARCH DESIGN AND METHODS

Study Design

PLIS (ClinicalTrials.gov identifier NCT01947595) is a stratified randomized multicenter trial involving eight study sites in university hospitals in Germany (Supplementary Table 1). Prediabetes was diagnosed from fasting and 2-h postchallenge glucose (2hPG) levels after a standardized oral glucose tolerance test (OGTT), according to the criteria of the American Diabetes Association (20). HbA_{1c} was not used as a definition for prediabetes. Screening procedures also involved measurement of liver fat content, insulin sensitivity, and insulin secretion. Based on previously established cutoff levels (16), these variables were used for risk stratification. HR participants were characterized by a reduced insulin secretion (disposition index [DI]) and/or insulin resistance (low insulin sensitivity index [ISI]) and elevated liver fat content. Cutoff levels for risk stratification (HR vs. LR) were $<$760 arbitrary units (AU) (DI, reduced insulin secretion), $<$9.2 AU (ISI, reduced insulin sensitivity), and $>$5.56% (liver fat content MRI) (16). For calculation of indices see Supplementary Material. LR participants were randomized to receive no LI (control group [LR-CTRL]) or a conventional LI (LR-CONV). HR participants were randomized to receive either a conventional LI (HR-CONV) or an intensive LI (HR-INT). Randomization was performed with a computer-based block randomization at the center of Tübingen by a study supervisor. For this, a self-devised randomizer with a permuted block randomization with a block size of 30 was used. At each study site, the study personnel were blinded, except for the principal investigator and the personnel performing the actual lifestyle counseling. Participants were enrolled between 2012 and 2016. The study protocol was approved by all local ethics committees of the participating institutions. This study has been reporting in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines, and the completed checklist can be found in Supplementary Material. The detailed study protocol is available online.

Study Outcomes

The primary outcome measure, 2hPG, was assessed with an OGTT after 12 months, and an intermediate OGTT was performed after 6 months. Secondary outcome measures were liver fat content, insulin sensitivity and secretion, and cardiovascular risk. Insulin sensitivity was calculated with glucose and insulin levels obtained during the OGTT with the equation of Matsuda and DeFronzo (ISI) (21). Insulin secretion was calculated with the insulinogenic index (IGI) (22). To obtain insulin secretion capacity adapted for the actual insulin sensitivity, we used the DI (ISI × IGI). Cardiovascular risk was assessed with the Framingham Risk Score, which was calculated with use of the equation provided by D'Agostino et al. (23), with participants having concomitant impaired fasting glucose and impaired glucose tolerance treated for this calculation as participants with diabetes.

Tertiary outcomes measures were adherence to the LI measures rated by a continuous score reaching from 0 to 5 (see below).

Participants

Individuals participated in a screening OGTT if they had clinically suspected prediabetes or at least 50 points in the German Diabetes Risk Score assessment battery (24). Basic inclusion criteria comprised age between 18 and 75 years, BMI <45 kg/m^2, and diagnosis of impaired fasting glucose and/or impaired glucose tolerance. Exclusion criteria are listed in Supplementary Table 2. All participants provided written informed consent.

Intervention

The duration of the LI was 12 months. In both the conventional and the intensified treatment groups, the LI was aimed at reaching a body weight reduction of 5% in participants with BMI >25 kg/m^2 through reduction of fat intake to $<30\%$ of total energy intake, reduction of saturated fat intake to $<10\%$ of total energy intake, and increase of fiber intake to >15 g/1,000 kcal total energy intake. Participants of the conventional intervention group received eight LI sessions in total over 1 year. They were advised to perform 3 h of exercise weekly. Participants of the intensified LI group received 16 coaching sessions in total over 1 year with advice to exercise 6 h weekly. The duration of the one-to-one coaching sessions was 30–60 min. They included dietary counseling based on diet protocols completed by the participants on four consecutive days. Furthermore, exercise counseling was performed on the basis of data from accelerometers, also enabling the assessment of accomplishing exercise goals. During each visit, lifestyle advisors graded adherence to the five goals of intervention (three diet goals, one exercise goal, and one weight reduction goal based on diet and exercise protocols and if a weight reduction $<5\%$ was reached). After 1 year of intervention, a total score was computed for all participants, with each of the five goals rated, as 1 when achieved and 0 if not, and aggregated. This sum score therefore ranges from 0 (none of the goals achieved) to 5 (all five goals achieved). All dietitians/lifestyle advisors were trained with the same curriculum (10 h) by a team from the primary site before starting recruitment. Refresher courses and face-to-face meetings between advisors were organized at least yearly between the study centers in workshops to ensure team building and harmonized counseling across all study sites involved. The LI was based on previously published established curricula (Diabetes Prevention Study [DPS], DPP, and TULIP [1,2,12]).

Participants of the control group only received a single 30-min one-to-one consultation with a dietitian at baseline.

OGTT and Analytical Procedures

OGTTs were performed at 8:00 A.M. after an overnight fast. Participants ingested 75 g glucose (Accu-Check Dextro O.G.T.; Roche). Blood samples were obtained at fasting and 30, 60, 90, and 120 min via an indwelling venous catheter. Blood samples were immediately put on ice and frozen at -80°C.

Glucose levels were measured locally at the study sites in certified laboratories with the glucose oxidase method. Plasma insulin was measured centrally in the laboratory of Tübingen University Hospital with a commercial chemiluminescence assay on an ADVIA Centaur XP (Siemens Healthineers, Eschborn, Germany). Clinical chemistry parameters (ALT and AST; γ-glutamyltransferase; HbA_{1c}; total, HDL, and LDL cholesterol; and triacylglycerol) were determined under quality-ensured conditions in the local routine diagnostic laboratories (see Supplementary Table 1), all certified by the German accreditation council (DAkkS). Internal and external quality assessments and proficiency testing were performed at all times of the study in each of these diagnostic laboratories. In the German Center for Diabetes Research (DZD) central clinical chemistry laboratory at Tübingen University Hospital, the above-mentioned analytes were measured on the ADVIA Chemistry XPT System (Siemens Healthineers) and Tosoh G8 HPLC analyzer (Tosoh Bioscience, Griesheim, Germany).

MRI and MRS

Liver fat content was determined by localized proton MRS (^{1}H-MRS) with use of stimulated echo acquisition mode in the posterior hepatic segment 7 (25). Liver fat content was determined by the ratio of signal integrals of fat (methylen + methyl signal) and total signal (water + fat), expressed as %. ^{1}H-MRS was not available in one center. Here, liver fat content was quantified by a chemical-shift selective imaging technique generating fat and water selective images (26). Liver fat content was determined from a manually drawn region of interest in segment 7, performed separately on the water selective and the fat selective image. Similar to the ^{1}H-MRS method, liver fat content was calculated as fat / (water + fat) * 100, with correction for relaxation effects to make the

imaging approach comparable with MRS. Both methodological approaches enable an accurate and comparable quantification of liver fat (27). For a small proportion of participants who were unable to undergo magnetic resonance studies or when magnetic resonance studies were not available, hepatic steatosis was assessed with use of ultrasound criteria to detect fatty liver as previously described (28) to allow for risk stratification.

Statistical Analysis

Given a type 1 error probability of 0.05 (α) and a type 2 error probability of 0.2 (β), the study was designed to be powered to detect a difference of 0.44 mmol/L in postchallenge glucose in a study population of 200 per intervention group. A complete cases approach was used for all analyses. We performed a sensitivity analysis after imputation of the missing variables using multivariable imputation performed on a wide data set encompassing basic variables (sex, age, BMI, waist circumference, education, study center) and glycemic variables (glucose during OGTT, glucose area under the curve [AUC], HbA_{1c}), variables on insulin secretion and sensitivity (ISI and IGI), and DI as well as liver fat content at baseline and follow-up at 12 months. The imputation was performed with the mice package in R with default settings (predictive mean matching as default algorithm, five iterations) and passive imputation for derived variables (DIs).

The primary and secondary end points were analyzed with general linear models. For example, as the primary end point, postchallenge glucose at the end of the intervention was evaluated with ANCOVA with the model terms intervention, baseline postchallenge glucose, and study center as fixed effects. For each other outcome at the follow-up visit, we used the outcome at baseline visit, intervention, and study center as model terms. Results from general linear models are provided as β estimates in *Results* and, for the specific intervention groups, as least squares means with 95% CI (Table 2). All other tables show means and SD. In addition, we have conducted post hoc tests using alternative insulin sensitivity and secretion variables to predict the primary outcome. The prediction power was very similar to our current approach; therefore, we think that the kind of indices estimating insulin sensitivity and secretion do not critically influence our results. Post hoc power analyses showed achieved statistical powers of 0.26 for the LR and 0.64 for the HR trials.

Due to follow-up visits at prespecified time points, we considered our data as interval censored for the computation of the regression to normal glucose tolerance. We approximated the baseline hazard with an exponential distribution and used this in full parametric proportional odds survival models in both risk groups.

All statistical analyses were performed in R (version 3.4) (29). Generalized linear models were fitted with the lm function in R with default settings, and the survival models were fitted with the icenReg package.

Data and Resource Availability

Information is provided in Supplementary Material.

RESULTS

Study Participants

Out of 2,561 individuals with increased risk for diabetes, a total of 1,160 were identified as eligible, agreed to participate, and underwent risk stratification into an LR group and an HR group. A total of 1,105 individuals were subsequently randomized into the four study groups and received allocated intervention. Details can be found in Fig. 1.

After 1 year, 908 individuals (82%) completed the study, and outcome data for the primary end point (complete glucose data from OGTT) were obtained. Among these individuals, HR subjects were significantly older and had higher BMI. They also differed in all major metabolic traits such as glucose and lipid levels, insulin sensitivity, and insulin secretion (see Table 1). The randomization procedure resulted in balanced demographic and clinical characteristics between LR-CTRL and LR-CONV as well as between HR-CONV and HR-INT (see Supplementary Table 4). Noncompleters did not differ from completers regarding the allocation to risk groups and intervention arms. Noncompleters significantly were more often female and younger and had higher BMI (see Supplementary Table 5).

Primary Outcome: Postchallenge Glucose

Postchallenge glucose levels decreased in all study groups (see Table 2).

The mean difference estimate between HR-CONV and HR-INT subjects of the change of postchallenge glucose levels from baseline to 1-year follow-up was −0.29 mmol/L (95% CI −0.54; −0.04, P = 0.025), with adjustment for baseline and center (see Fig. 2*A*). For the least squares means of changes from baseline to follow-up in each intervention group, see Table 2. The change in 2hPG was not significantly different between the LR-CTRL and LR-CONV groups (mean difference estimate 0.19 mmol/L [95% CI −0.22; 0.60, P = 0.4]) (see Fig. 2*A*).

Regression to Normal Glucose Tolerance During Long-term Follow-up

We extended our study to perform follow-up visits after the LI, including an OGTT after 1 and 2 years. During this total observation period of 3 years, intensive LI led to a cumulative higher conversion rate to normal glucose tolerance in HR individuals in comparisons with conventional LI (hazard ratio 1.57 [95% CI 1.17; 2.1, P = 0.003]; parametric proportional odds survival model with use of an exponential baseline risk distribution [Fig. 3]). Among LR individuals, LR-CONV participants had a higher chance of conversion to normal glucose tolerance than LR-CTRL

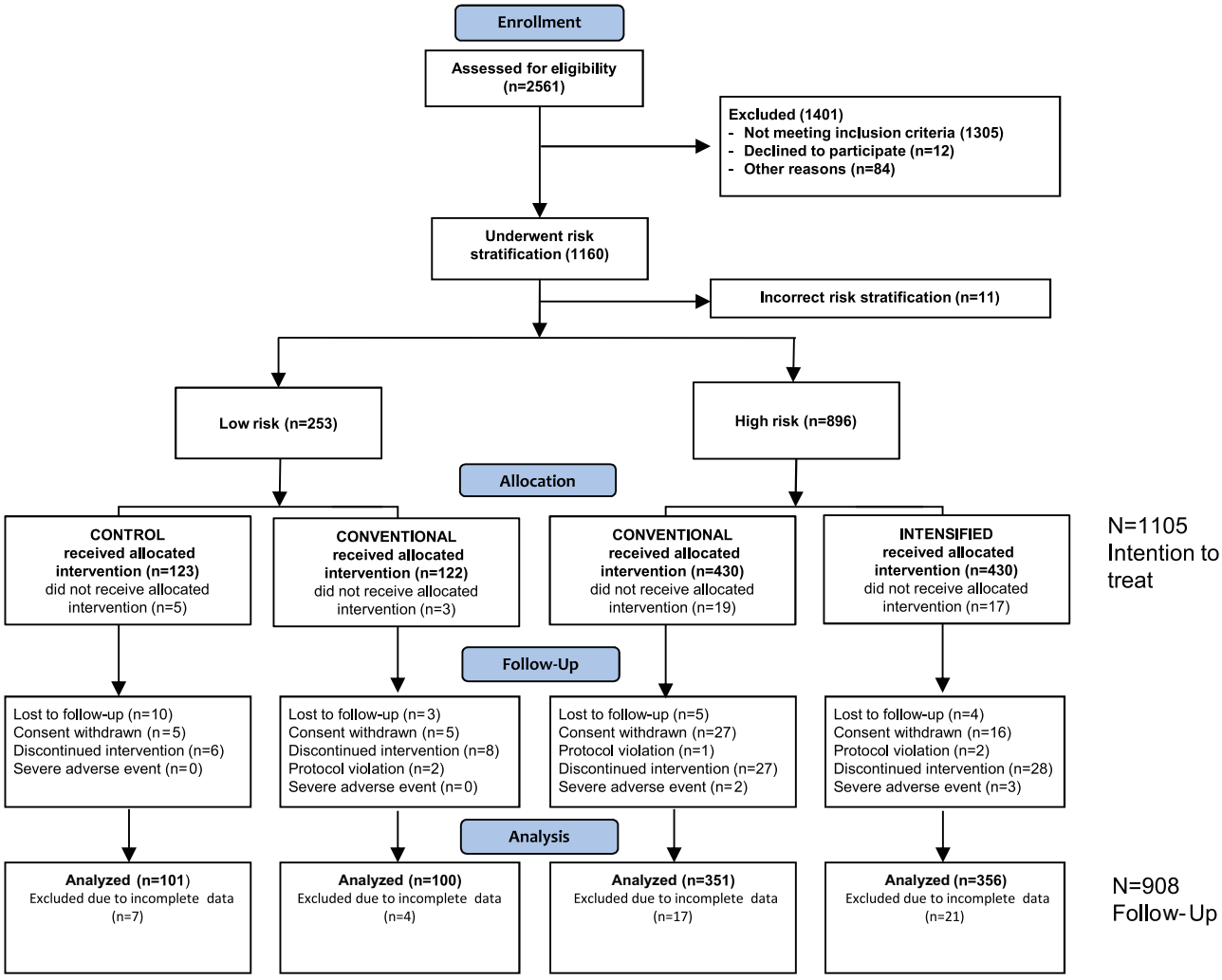

Figure 1—Participant flow during the study (CONSORT diagram).

subjects during 3 years of follow-up (hazard ratio 2.02 [95% CI 1.18; 3.43, P = 0.01]).

Secondary Outcomes (BMI, Insulin Sensitivity and Secretion, Liver Fat Content, Cardiometabolic Risk) and Sensitivity Analysis

The mean difference estimate between HR-INT and HR-CONV participants for the change in liver fat content was −1.34% (95% CI −2.17; −0.5, P = 0.002). For cardiometabolic risk score, this difference was −1.82 (95% CI −3.13; −0.5, P = 0.007), for insulin sensitivity 0.64 AU (95% CI 0.13; 1.15, P = 0.01), and for BMI −0.47 kg/m^2 (95% CI −0.74; −0.2, $P < 0.001$) in the HR-INT group compared with the HR-CONV group after 1 year of LI (see Table 2 and Fig. 2). The change in insulin secretion was similar in the HR-CONV and HR-INT groups.

There were no statistically significant differences between LR-CONV and LR-CTRL subjects, except in the case of BMI and fasting glucose (see Table 2).

As sensitivity analysis, we imputed all missing variables for the baseline and follow-up visit and computed the main outcomes in the imputed data set. The significance levels of the results were consistent with those of the analysis of complete cases (see Supplementary Table 3), but effect sizes tended to be higher.

Adherence

The main study outcome, 2hPG, was associated with the aggregate percentage of completed lifestyle goals (both modeled as continuous variable, analyzed in a baseline-adjusted linear model, β ± SE −0.09 ± 0.03, P = 0.001). In a baseline-adjusted multivariable model comprising all specific lifestyle goals, only achievement of weight reduction (−0.18 ± 0.03, $P < 0.001$) and exercise goals (−0.07 ± 0.03, P = 0.02) was independently associated with 2hPG. In addition, the number of completed visits during the study was also positively associated with 2hPG in a model with adjustment for baseline postchallenge glucose and intervention (−0.23 ± 0.1, P = 0.02).

Table 1—Comparison of baseline parameters of the LR vs. HR group (individuals with complete follow-up)

	LR	HR	*P*
Female/male sex, *n* (%)	124/77 (62/38)	395/312 (56/44)	0.16
Age (years)	57 ± 11	59 ± 10	0.057
Weight (kg)	80.7 ± 16.2	92.2 ± 19.4	<0.0001
BMI (kg/m^2)	28.1 ± 5.2	31.7 ± 5.8	<0.0001
Waist circumference (cm)	94 ± 12	105 ± 14	<0.0001
Waist-to-hip ratio	0.89 ± 0.08	0.94 ± 0.08	<0.0001
Systolic blood pressure (mmHg)	135 ± 17	140 ± 17	0.0013
Diastolic blood pressure (mmHg)	84 ± 11	86 ± 11	0.043
Fasting glucose (mmol/L)	5.7 ± 0.4	6.0 ± 0.5	<0.0001
Postchallenge glucose (mmol/L)	6.8 ± 1.5	7.8 ± 1.7	<0.0001
Glucose AUC (mmol/min/L)	934 ± 121	1,131 ± 160	<0.0001
Glycated hemoglobin (%)	5.6 ± 0.3	5.8 ± 0.3	<0.0001
Glycated hemoglobin (mmol/mol)	38.1 ± 3.6	39.7 ± 3.8	<0.0001
Triglycerides (mmol/L)	1.25 ± 0.85	1.63 ± 0.96	<0.0001
Cholesterol (mmol/L)	5.28 ± 0.87	5.44 ± 1.05	0.026
LDL cholesterol (mmol/L)	3.17 ± 0.81	3.34 ± 0.91	0.013
HDL cholesterol (mmol/L)	1.51 ± 0.57	1.38 ± 0.39	0.0025
Liver fat content (%)	2.85 ± 2.92	10.45 ± 8.19	<0.0001
ISI (AU)	9.96 ± 5.09	5.61 ± 3.06	<0.0001
Insulin secretion (DI) (AU)	1,533 ± 1,187	671 ± 467	<0.0001
Hypertension, no/yes, *n* (%)	119/72 (62/38)	307/366 (46/54)	<0.0001
Hyperlipidemia, no/yes, *n* (%)	113/72 (61/39)	355/290 (55/45)	0.17
History of myocardial infarction, no/yes, *n* (%)	188/4 (98/2)	639/17 (97/3)	0.89
History of stroke, no/yes, *n* (%)	185/6 (97/3)	636/17 (97/3)	0.88
Peripheral artery disease, no/yes, *n* (%)	173/13 (93/7)	572/80 (88/12)	0.059
Medication, no/yes, *n* (%)			
ACE inhibitors	180/21 (90/10)	593/114 (84/16)	0.06
Angiotensin receptor blockers	168/33 (84/16)	536/171 (76/24)	0.026
Thiazide diuretics	185/16 (92/8)	607/100 (86/14)	0.028
Other diuretics	196/5 (98/2)	676/31 (96/4)	0.31
β-Blockers	174/27 (87/13)	545/162 (77/23)	0.0048
Statins	175/26 (87/13)	581/126 (82/18)	0.13
Current smoking, no/yes, *n* (%)	184/10 (95/5)	645/44 (94/6)	0.64
Alcohol consumption, *n* (%)			0.054
None	31 (16)	71 (10)	
Rarely	73 (37)	304 (45)	
Weekends	14 (7)	57 (8)	
2–3 times weekly	60 (31)	169 (25)	
Daily	18 (9)	84 (12)	
Highest education, *n* (%)			0.067
None	5 (3)	19 (3)	
Postsecondary	99 (50)	314 (46)	
Bachelor's degree or equivalent	33 (17)	174 (26)	
Master's degree or equivalent	60 (30)	172 (25)	

Data are means ± SD unless otherwise indicated.

Table 2—Changes of key study variables between baseline and follow-up in LR (LR-CTRL vs. LR-CONV) and HR (HR-CONV vs. HR-INT) individuals

	LR			HR		
	LR-CTRL	LR-CONV	*P***	HR-CONV	HR-INT	*P***
Number	101	100		351	356	
Weight (kg)	−0.5 (−1.0; 0.3)	−2.2 (−3.0; −1.4)	<0.0001	−2.5 (−3.2; −1.9)	−4.0 (−4.6; −3.3)	<0.0001
BMI (kg/m^2)	−0.2 (−0.5; 0.1)	−0.8 (−1.1; −0.5)	<0.0001	−0.9 (−1.1; −0.7)	−1.3 (−1.6; −1.1)	<0.0001
Fasting glucose (mmol/L)	−0.07 (−0.17; −0.03)	−0.21 (−0.32; −0.11)	0.02	−0.17 (−0.23; −0.11)	−0.26 (−0.32; −0.19)	0.03
Postchallenge glucose (mmol/L)	−0.36 (−0.71; −0.00)	−0.54 (−0.89; −0.19)	0.4	−0.48 (−0.69; −0.28)	−0.77 (−0.98; −0.57)	0.03
Glucose AUC (mmol/min/L)	−1 (−33; 31)	−31 (−62; 1)	0.1	−66 (−85; −46)	−92 (−111; −73)	0.03
Glycated hemoglobin (%)	−0.0 (−0.1; 0.0)	−0.0 (−0.1; 0.0)	0.6	−0.1 (−0.1; −0.1)	−0.1 (−0.1; −0.2)	0.02
Glycated hemoglobin (mmol/mol)	−0.3 (−1.0; 0.3)	−0.5 (−0.9; 0.2)	0.6	−1.0 (−1.5; −0.7)	−1.5 (−0.8; −1.1)	0.02
ISI (AU)	−0.7 (−1.6; 0.2)	0.3 (−0.6; 1.1)	0.06	1.3 (0.9; 1.7)	2.0 (1.6; 2.4)	0.01
Insulin secretion (DI) (AU)	−198 (−459; 63)	−46 (−307; 216)	0.3	247 (151; 343)	260 (166; 355)	0.8
Liver fat content (%)***	0.0 (−0.5; 0.6)	−0.2 (−0.8; 0.4)	0.4	−2.6 (−3.3; −1.8)	−3.9 (−4.6; −3.2)	0.002
Framingham, 10-year CV risk (%)	−0.4 (−1.9; 1.0)	−1.0 (−2.4; 0.4)	0.5	−2.0 (−3.0; −0.9)	−3.8 (−4.9; −2.8)	0.007

Unless otherwise indicated, data are least squares means (95% CI) of changes from baseline to follow-up (1 year). CV, cardiovascular; Framingham, Framingham Risk Score. **ANCOVA adjusted for baseline and center. ***Measured at both baseline and follow-up in *n* = 631 individuals. LR-CTRL, *n* = 72; LR-CONV, *n* = 74; HR-CONV, *n* = 241; HR-INT, *n* = 244.

The aggregate percentage of completed lifestyle goals was higher in the LR-CONV than in the HR-CONV group (mean ± SD 45 ± 3% vs. 38 ± 1%, $P = 0.03$, Wilcoxon rank sum test [Supplementary Fig. 2]). The aggregate percentage of completed lifestyle goals was similar in the HR-CONV (38 ± 1%) and the HR-INT (41 ± 1%, $P = 0.5$, Wilcoxon rank sum test) groups. In investigations of the specific goals within the HR groups, more individuals reached exercise goals in the HR-CONV group and the weight goals were achieved by more individuals in the HR-INT group (both $P < 0.001$, χ^2 test).

Safety and Adverse Events

There were 0.88 adverse events per patient-year. After adjustment for the number of visits and for centers, the frequency of adverse events was not different between all four risk groups (all $P > 0.5$, Poisson regression). No severe adverse events were recorded during the trial.

DISCUSSION

In the present multicenter, risk-stratified, randomized controlled lifestyle intervention trial, our primary aim was to test whether individuals with prediabetes and an HR phenotype with impaired insulin secretion and/or insulin resistant fatty liver benefit from an intensification of conventional LI. PLIS showed that in this population at high risk for diabetes, intensification of LI through increase of counseling frequency and weekly physical exercise indeed yielded a superior improvement of the primary outcome, i.e., postprandial glucose metabolism after 1 year of LI. In addition, these participants undergoing intensive LI were also more likely to have reduced secondary outcomes such as liver fat content and cardiometabolic risk. In a second randomized trial within PLIS, we additionally tested whether individuals with an LR phenotype benefit from conventional LI compared with no LI. In these participants, we detected no difference of the primary outcome, postprandial glucose metabolism. However, a smaller sample size in the LR stratum resulting in a low power might have precluded detection of smaller differences.

The stratification between the LR and HR phenotype is defined by pathophysiological features of type 2 diabetes and has previously been described (12,16,17). The determinants of this phenotype, impaired insulin secretion and insulin resistance, are the main pathomechanisms for the development of type 2 diabetes (30–34).

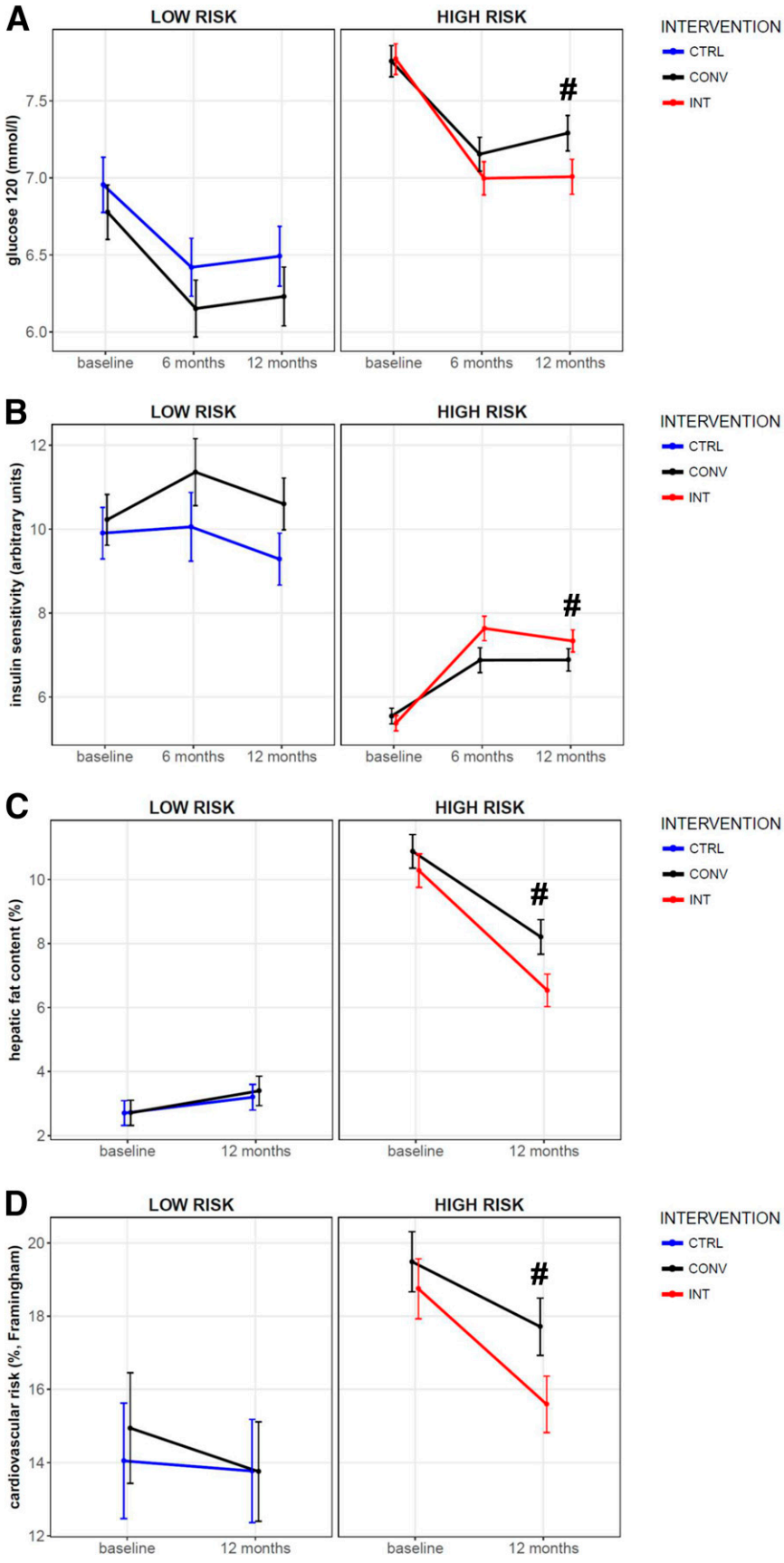

Figure 2— Plasma glucose levels at 120 min after standardized 75-g glucose challenge (*A*) and insulin sensitivity (*B*) at baseline and 6 and 12 months during LI and hepatic fat content (*C*) and cardiometabolic risk (*D*) at baseline and 12 months during LI. Values are shown as least squares means and SEs, with adjustment for study center. Framingham, Framingham Risk Score. #Significant difference ($P < 0.05$) between HR-CONV and HR-INT in change of the parameter from baseline.

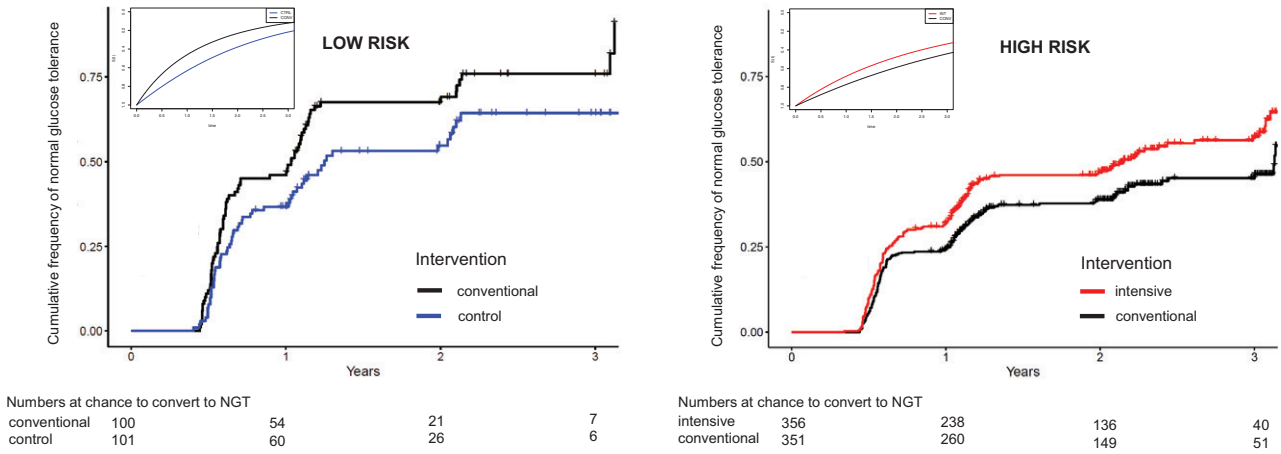

Figure 3—Results after 3 years' observation (1 year of lifestyle intervention and additional 2 years of follow-up). Cumulative frequency of normal glucose tolerance in LR (left panel) (log-rank test $P = 0.03$) and HR (right panel) (log-rank test 0.008) individuals. The inserts represent parametric survival models using fits of interval-censored data. $P = 0.01$ for the LR-CONV vs. LR-CTRL group (left panel) and $P = 0.003$ for the HR-INT vs. HR-CONV group (right panel).

Our data indicate that conventional lifestyle interventions, as were applied in the DPS (1) and DPP (2), can be successfully intensified. This argues for a dose-effect relationship in LI. With application of the intensified intervention, beneficial effects on BMI, insulin sensitivity, and liver fat content were more pronounced. In contrast, intensified LI did not improve insulin secretion capacity in comparison with conventional LI (Table 2 and Supplementary Fig. 1). Therefore, the superior effect of intensified LI on postchallenge glucose seems mainly due to reduced liver fat content and improved insulin sensitivity. The changes of liver fat content and insulin sensitivity were significantly associated with improvement of glucose tolerance, independent of change in body weight in the HR population ($\beta = 0.045$, $P = 0.02$, and $\beta = -0.12$, $P < 0.0001$, respectively). The importance of improved insulin sensitivity in successful LI is consistent with findings from the DPP and DPS trials (35,36), whereas the data about the role of liver fat reduction are new.

The intensified and conventional intervention in PLIS differed with regard to exercise volume and the amount of counseling sessions. Of note, the number of completed visits and the accomplishment of the weight reduction goal were significantly associated with the reduction of 2hPG during 1 year of intervention in all treatment groups. This suggests that the amount of counseling and either more motivation or more guidance from lifestyle advisors underlie the higher efficacy of the intensive treatment group. Qualified lifestyle counsellors and an adequate counseling frequency should be key factors in LI planning. Additional important factors are the perception and quality of life of participants taking part in the different lifestyle interventions. Quality of life during long-term follow-up and the feasibility of such lifestyle intervention in a real-world situation are being analyzed in a separate project.

One feature of PLIS was that we additionally tested the effect of conventional LI in the LR group for LI nonresponse by comparing the LR-CONV group with the LR-CTRL group. No difference was found for the primary end point 2hPG between those groups. However, based on the limited statistical power reached in the LR group due to the smaller sample size of this group, we cannot exclude a false negative finding with acceptable confidence.

Several studies have shown that translating the promising results of controlled lifestyle interventions into a real-world scenario is hardly possible (37,38). Risk stratification during screening and subsequent allocation of resources to individuals who are at marked risk may improve outcomes and cost-effectiveness. For example, among individuals with type 2 diabetes no advantage of an LI for cardiovascular disease mortality or morbidity was shown in Look AHEAD (Action for Health in Diabetes) (39). However, in a post hoc analysis investigators recently identified a subgroup who benefited from the LI. Individuals with well-controlled diabetes (LR) and poor self-reported general health did not benefit from the intervention (40). A screen-and-treat policy for the prevention of type 2 diabetes will be effective when it is possible to prospectively identify HR individuals while excluding LR individuals (41). The current study provides a proof of concept for this approach.

Importantly, the beneficial effects of intensified LI reach beyond glucose control. The current study is the largest multicenter randomized LI trial with measurement of liver fat content with a highly reliable technique of MRS. Hepatic steatosis is present in 25% of the adult population in the U.S. and is associated with diabetes, cardiovascular disease, steatohepatitis, and liver cancer (42). Among HR individuals, we achieved a relative liver fat reduction of 37% in HR-INT, whereas the HR-CONV group only had a relative reduction of 24%. The HR-INT group achieved reduced liver fat

content of 6.6 ± 0.5% compared with 8.3 ± 0.5% (mean ± SD) in the HR-CONV group. This means that liver fat content was close to the normal threshold of 5.6% after the intensified intervention, implying a clinically relevant effect—a target for future approaches to diabetes prevention.

Furthermore, the cardiovascular risk diminished in the participants of the HR stratum, with a near doubling of risk reduction for the HR-INT group compared with that of the HR-CONV group (see Table 2 and Fig. 2).

Limitations of our study include the relative short LI duration of 12 months and a noncompleter rate of 18% after 1 year. The latter is, however, well in the range of other LI studies with rates between 5 and 28% (5). A potential further limitation is the heterogeneity of lifestyle counseling throughout different study centers, which could have been reduced by more frequent meetings and interactions between study sites. Furthermore, the design of the current study did not include an intensified intervention in the LR group, so we were unable to test whether the intensified LI would work in LR individuals. Therefore, it may be possible that the level of physical activity was not sufficient to improve outcomes in this group. In addition, there was not a control group, without intervention, for HR. Moreover, the HR and LR groups were unbalanced, with more individuals stratified to the HR group (78%). Thus, one of the predefined questions, "Is lifestyle intervention effective in LR individuals with prediabetes?", cannot be answered with high confidence in the current study due to a low statistical power reached in this group.

To our knowledge, this is the first multicenter study where investigators prospectively tested different intensities of lifestyle intervention in a risk-stratified manner. PLIS confirms the existence of an HR phenotype for nonresponse to LI in individuals with prediabetes. This nonresponse can be partially compensated with intensified LI such that a higher percentage of HR individuals improve glucose metabolism and decrease liver fat content and cardiovascular risk. Finally, conventional lifestyle intervention with the aim of improving glucose tolerance in LR individuals with prediabetes might also be important. Future studies are needed to explicitly investigate this question in LR individuals. Nonetheless, screen-and-treat approaches in the prevention of type 2 diabetes should include risk stratification and individualized interventions.

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