

Article

Predicting Factors for Metabolic Non-Response to a Complex Lifestyle Intervention—A Replication Analysis to a Randomized-Controlled Trial

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Abstract: Background: T2DM heterogeneity affects responsiveness to lifestyle treatment. Beta-cell failure and nonalcoholic fatty liver disease (NAFLD) independently predict T2DM, but NAFLD inconsistently predicts metabolic response to lifestyle intervention. Aim: We attempt to replicate a prediction model deduced from the Tübinger Lifestyle Intervention Program by assessing similar metabolic factors to predict conversion to normal glucose regulation (NGR) in a comparable lifestyle intervention trial. Methods: In the Optimal Fiber Trial (OptiFiT), 131 Caucasian participants with prediabetes completed a one-year lifestyle intervention program and received a fiber or placebo supplement. We compared baseline parameters for responders and non-responders, assessed correlations of major metabolic changes and conducted a logistic regression analysis for predictors of remission to NGR. Results: NGR was achieved by 33 participants, respectively. At baseline, for the placebo group only, 1 h and 2 h glucose levels, glucose AUC and Cederholm index predicted conversion to NGR. HOMA-beta, HOMA-IR or liver fat indices did not differ between responders and non-responders of the placebo or the fiber group. Changes in waist circumference or fatty liver index correlated with changes in glycemia and insulin resistance, but not with changes in insulin secretion. Insulin-resistant NAFLD did not predict non-response. Differences in compliance did not explain the results. Conclusions: Higher post-challenge glucose levels strongly predicted the metabolic non-response to complex lifestyle intervention in our cohort. Depending on the specific intervention and the investigated cohort, fasting glucose levels and insulin sensitivity might contribute to the risk pattern. Beta-cell function did not improve in accordance with other metabolic improvements, qualifying as a potential risk factor for non-response. We could not replicate previous data suggesting that an insulin-resistant fatty liver is a specific risk factor for treatment failure. Replication studies are required.

Keywords: diabetes mellitus type 2; prediabetes; diabetes prevention; impaired fasting glucose; impaired glucose tolerance; insoluble dietary fiber; insulin sensitivity; insulin secretion; NAFLD; response prediction

1. Introduction

The type 2 diabetes mellitus (T2DM) epidemic is continuously growing, threatening patients with premature death and morbidity, characterized by cardiovascular disease, cancer and various other long-term complications. About 50% of the disorder is attributed to genetic influences and family history, and the other half is believed to be responsive to prevention and treatment including lifestyle measures [1–3]. T2DM is partially caused and thereby partially treatable by changes in eating behavior, physical activity and other lifestyle factors. Large prevention trials in Caucasian and Asian cohorts have consistently demonstrated that the implementation of a complex lifestyle intervention can result in a risk reduction of diabetes incidence of about 40–60% [4–7]. These interventions include weight loss for overweight and obese prediabetes patients [8], increased physical activity and improvement of specific nutritional factors such as the reduction of saturated fat, sugars and other simple carbohydrates, alcohol and increased intake of cereal fiber [9]. In Germany, the one-year PREDIAS program combines all of these factors [10].

Recently, several publications on prediabetes and overt T2DM characterized a scheme of metabolic heterogeneity in large non-interventional cohorts by defining diabetes subphenotypes, defined by glycemic state, insulin sensitivity and insulin secretion, liver fat and BMI. Hereby, subjects with a predominant lack of insulin production and others with considerable insulin resistance are burdened with the greatest risk for diabetes complications [11,12]. Similarly, in smaller prediabetes cohorts, isolated impaired fasting glucose (IFG) leads to a lower risk of diabetes onset compared to impaired glucose tolerance (IGT), even though IFG is more strongly associated with unhealthy lifestyle, obesity and NAFLD [13–17]. NAFLD itself predicts prediabetes and T2DM onset in observational settings [18–22]. Beta-cell dysfunction is also considered an independent risk factor for progression to overt T2DM as shown by postprandial glucose levels or other measures of insulin secretion [23].

For T2DM, intervention studies have only sparsely reported results on subgroup specific responsiveness to lifestyle treatments. In previous diabetes prevention trials, stratification by IFG and IGT status indicated subtype-specific responses to lifestyle treatments, consistently showing the NAFLD-prone IFG patients achieve better improvements in response to low-fat or fiber-rich diets [24–29]. In support of these findings, elevated transaminase levels predicted diabetes progression in the control group of the J-DOIT1 trial, but a better response to lifestyle intervention [30]. Even though all of these studies indicated a particularly good response of patients with NAFLD surrogates to lifestyle treatment, none of them actually measured liver fat content [24–29].

The Tübinger Lifestyle Intervention Program (TULIP), investigating a 9-month complex lifestyle intervention (diet and exercise) in patients at elevated risk for T2DM, was the first prediabetes study directly assessing liver fat content by magnetic resonance spectroscopy. The authors confirmed impaired insulin secretion as a risk factor for metabolic inertia towards lifestyle changes, but also identified the presence of an insulin-resistant NAFLD as a high-risk condition, which contradicts the findings of earlier studies [24–29]. In TULIP, insulin sensitivity and liver fat improved in parallel to weight loss, while insulin secretion did not. In a logistic regression analysis, both low insulin secretion and insulin-resistant NAFLD qualified as independent risk factors for metabolic non-response. Based on their sophisticated risk stratification, subjects with at least one of the two risk factors have a 4-fold risk of not achieving normal glucose regulation (NGR) [31]. Up to now, this surprising result, which contradicts larger, earlier prevention studies [24–29], has not been replicated. Doing this is a difficult task, as other prediabetes studies differed in the length of intervention, characteristics of the diet, absence of exercise recommendations [4–7] and lack of MR liver fat measurements.

The Optimal Fiber Trial is a German diabetes prevention study of similar cohort size, which used a comparable intervention schema [32]. In our present paper, we aim to assess whether data from OptiFiT can replicate the findings of TULIP, using the exact same statistical approach and scheme of presentation as the original paper [31]. We expect

weaker correlations between weight loss and the change in insulin secretion (compared to insulin sensitivity), as well as an independent association of low insulin secretion and insulin-resistant NAFLD with the non-remission of prediabetes.

2. Research Design and Methods

Recruitment, inclusion and exclusion criteria as well as the overall study design of OptiFiT have been published elsewhere [32]. OptiFiT entailed 180 adult subjects with impaired glucose tolerance (IGT), 78% of which fulfilled the definition of Metabolic Syndrome [33]. Patients with severe comorbidities or secondary origin of glycemic alterations were excluded. The study was approved by the ethics committees of the University of Potsdam and the Charité University Hospital Berlin (both under approval code EA4/192/09). OptiFiT was conducted in accordance with the Declaration of Helsinki and GCP-ICH. All subjects provided written informed consent prior to their participation. OptiFiT, the Optimal Fiber Trial, was registered at clinicaltrials.gov: NCT01681173 (first registered on 7 September 2012).

In total, 131 subjects (fiber: $n = 64$; placebo: $n = 67$; 60 ± 9 years, BMI 32.7 ± 5.9 kg/m², 62% female) completed the first year of intervention and provided all data necessary for this particular post-hoc analysis for the replication of TULIP with a comparable cohort size. The selected 1-year time frame also provided the best comparability to the 9-month intervention of TULIP (Figure 1).

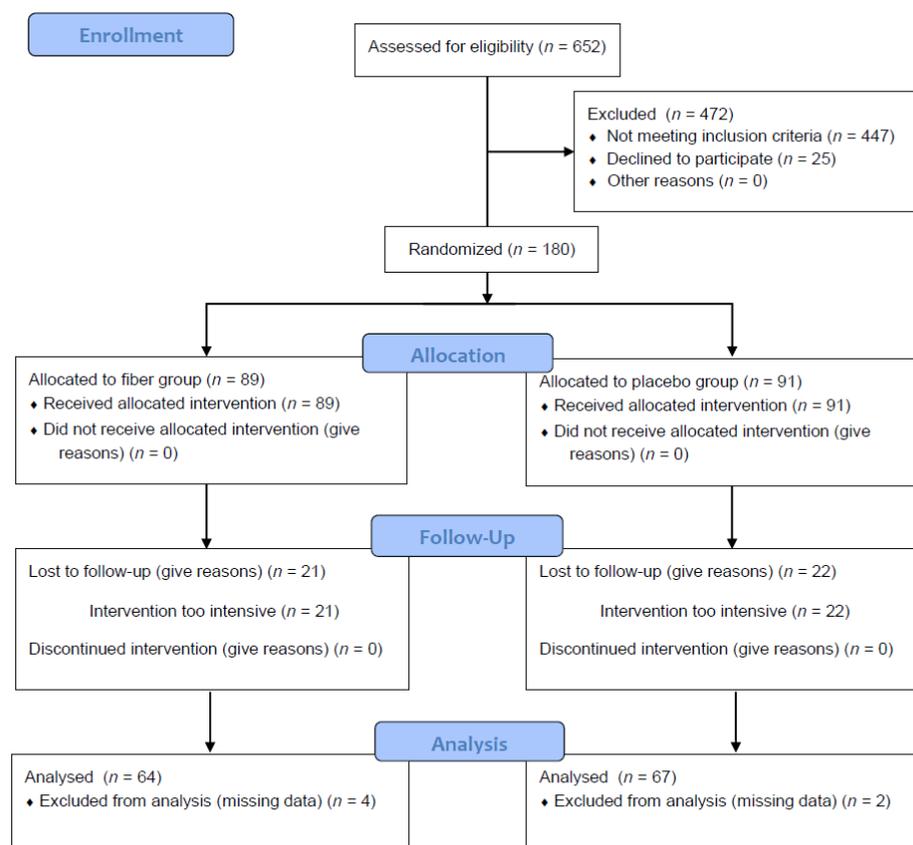


Figure 1. CONSORT flow diagram.

All participants had started our 24-month study with a modified version of the one-year lifestyle program PREDIAS, which was a structured “Treatment and Education Program for Prevention of type 2 diabetes”. PREDIAS contained group-based consultations at regular intervals and consisted of 12 individual 2 h lessons divided into a core intervention (8 lessons in 8 weeks) and booster sessions (4 lessons throughout the following 10 months) [10,34]. For OptiFiT, an adapted approach was applied by defining goals for

change in diet quality in accordance with the recommendations of the German Society for Nutrition (DGE): fat intake below 30 kcal%, intake of saturated fat below 10 kcal% and intake of dietary fiber of at least 15 g/1000 kcal. We also aimed for higher levels of physical activity (240 min/week), which is above the original PREDIAS recommendation (150 min/week) [10]. We motivated our patients to consume whole-grain products, legumes, vegetables, fruits, and in particular berries, low-fat milk and meat products, soft margarines and vegetable oils rich in unsaturated fatty acids. Physical activity was monitored by pedometers and the IPAQ-2 questionnaire [35].

Our participants completed food records for four consecutive days, including one weekend day, on baseline and every six months from that. Nutrient intake was determined using the nutrition software PRODI[®] 5.8 based on Bundeslebensmittelschlüssel 3.0 [36].

For 24 months, subjects received a blinded supplement, which contained either 70 wt% cellulose, 25 wt% hemicellulose and 3–5 wt% lignin from oat hulls (verum; Vitacel OF 560–30; Rettenmaier & Soehne Inc., Holzmuehle, Germany), adding 15 g of mainly insoluble fiber per day to the normal nutrition, or consisted of waxy maize starch with negligible content of insoluble fiber (1.6 g per day; placebo). Further details on the supplementation procedure, measurements and laboratory parameters have been given elsewhere [32].

Metabolic state was assessed by oral glucose tolerance tests (oGTT) with half-hourly capillary glucose measurements for two hours. From these tests, serum levels for insulin and c-peptide were derived every hour, and areas under the curve (AUC) for capillary glucose, insulin and c-peptide were calculated by the trapezoidal method.

For TULIP, which we wanted to replicate, subjects were classified on the basis of arbitrary cut-off values (medians) for whole-body insulin sensitivity (Matsuda index) and for insulin secretion capacity (disposition index) as well as by the validated cut-off for NAFLD (MR spectroscopy, >5.56%) [31,37–39]. In our study, due to budget reasons, oGTT measurements for insulin included only limited (hourly) time points; therefore, neither the disposition index nor Matsuda index could be calculated. Additionally, MR spectroscopy was only available for a small subgroup (26% of the cohort) [40]. Therefore, we used the Cederholm index [41] to quantify insulin sensitivity and the HOMA-beta to assess insulin secretion [42], as those could be calculated with our limited set of serum blood samples (0', 60', 120'). The fatty liver index (FLI) was calculated according to the primary publication [43]. Following the TULIP approach, we classified patients by median splits for insulin resistance and insulin secretion. The established cut-off for fatty liver (in our case: FLI > 60) defined the presence of NAFLD.

In the TULIP study, subjects were classified as responders when achieving “NGR”. In our study, subjects were also classified as “NGR” (responders) if they achieved normalization of both fasting (<90 mg/dL capillary glucose levels) and the post-challenge glucose (<140 mg/dL capillary glucose levels) after one year. All subjects who failed to achieve this normalization were labelled “prediabetes/T2DM” (non-responders). As the major inclusion criterion of our study was the presence of IGT, we tested an alternative response classification, comparing those who achieved normalization of post-challenge glucose after one year, irrespective of (non-diabetic) fasting glucose levels (“NGT”; responders), with subjects failing to achieve normalization of post-challenge glucose levels (“IGT/T2DM”, non-responders).

Statistical Analyses

We used the Kolmogorov–Smirnov test in order to determine the normal distribution of our data. Given the frequent absence of normal distribution, we decided to conduct non-parametric tests (Mann–Whitney tests) to compare major metabolic parameters at baseline and indicators of lifestyle compliance between the responders and non-responders for both intervention arms separately. For correlations, the non-parametric Spearman approach was chosen. Comparisons between post-hoc defined risk groups were made by ANCOVA (adjusted for sex, age, baseline levels), following the original publication of TULIP [31]. In addition, in analogy to the TULIP analysis, a multivariate logistic regression model

was used to identify binary factors predicting non-response [31]. We included age, BMI, waist circumference, fasting and 2 h glucose, liver fat (fatty liver index), insulin secretion (HOMA-beta) and insulin sensitivity (Cederholm index) as continuous variables, and sex and the presence of insulin-resistant fatty liver (Cederholm index below the median and FLI > 60) as independent categorial variables.

All data were presented as means \pm standard deviation. The results were considered significantly different if $p < 0.05$. All statistical analyses were performed using SPSS for Windows program version 25.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Cohort Structure

At baseline, out of the 131 eligible subjects, 65 subjects were classified as insulin-deficient (HOMA-beta < 74.6) and 66 as insulin-sufficient (HOMA-beta > 74.6); 65 participants were considered to be whole-body insulin-resistant (Cederholm < 35.1) and 66 as whole-body insulin-sensitive (Cederholm > 35.1). NAFLD was assumed in 93 subjects (FLI > 60), while 38 subjects had FLI values that were either indicative of the absence of NAFLD (<30) or inconclusive for classification (30–60). In total, 28 subjects (21%) had neither insulin-resistant NAFLD nor an insulin secretion deficit and would resemble the “low-risk” phenotype of TULIP, while the remaining 103 subjects combined (79%) were representative of the TULIP “high-risk” phenotype. In total, 57 subjects with NAFLD were insulin-resistant. Of those, 19 had an additional beta-cell dysfunction (HOMA-beta < 74.6), while 38 had an insulin-resistant NAFLD with preserved insulin secretion capacity [31]. See Figure 2 for an overview of the cohort structure.

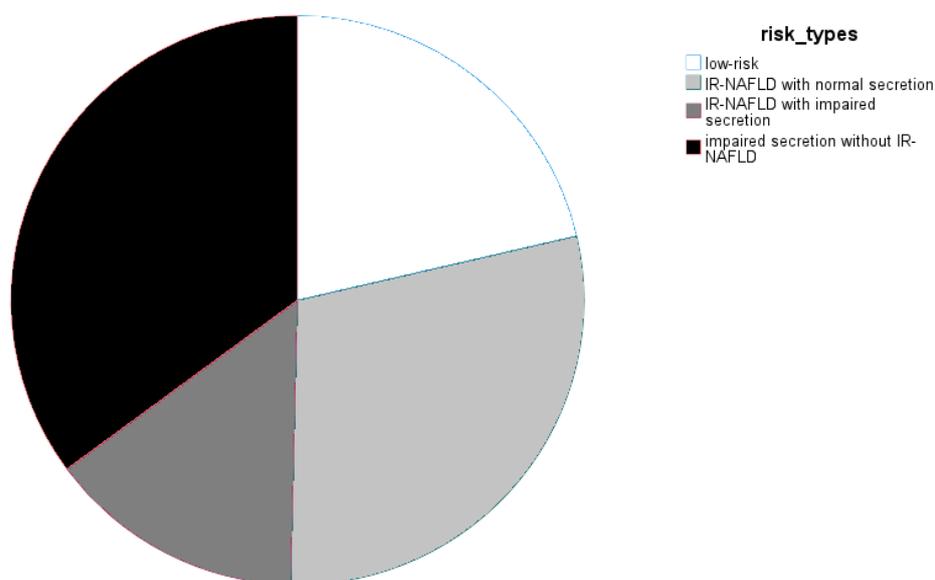


Figure 2. Cohort structure of OptiFiT according to the stratification schema, derived from the TULIP study.

3.2. Intervention Effects and Factors Predicting Achievement of NGR

After one year, in the fiber group, NGR was achieved by 14 subjects. In the placebo group, one-year conversion to NGR was found in 19 subjects. Although there was no significant difference in the frequency of NGR between the fiber and placebo groups, there were significant differences in HbA1c and 2 h glucose levels as shown before [32].

Lower 1 h and 2 h glucose levels and glucose AUC as well as a higher Cederholm index were predictive for conversion to NGR (Table 1, first columns) in the placebo group. In the fiber group, lower 2 h glucose levels, exclusively and only trend-wise, were predictive for conversion to NGR (Table 1, middle columns). When combining the fiber and placebo groups, lower 2 h glucose and glucose AUC were significantly, and a higher Cederholm

index was trend-wise associated with regression to NGR (Table 1, last columns). The results for both groups (separately and combined) were similar, when evaluating the conversion to NGT rather than NGR (Table A1). Neither in the two intervention arms separately, nor in the total cohort, did measures for fasting insulin sensitivity (HOMA-IR), insulin secretion (HOMA-beta) and liver fat (fatty liver index, estimated liver fat) differ significantly between responders and non-responders.

Table 1. Characteristics of responders and non-responders (NGR) at study entry; Mann–Whitney tests for comparison of NGR and non-NGR subgroups.

Characteristics of Participants at Study Entry	Placebo Arm			Fiber Arm			Full Cohort		
	NGR (n = 19)	No NGR (n = 48)	p-Value	NGR (n = 14)	No NGR (n = 50)	p-Value	NGR (n = 33)	No NGR (n = 98)	p-Value
Cohort Structure									
Age	61 ± 10	60 ± 9	n.s.	58 ± 10	60 ± 9	n.s.	59 ± 10	60 ± 9	n.s.
Sex	63%	48%	n.s.	64%	74%	n.s.	64%	61%	n.s.
Anthropometry									
Weight (kg)	91.8 ± 22.3	94.5 ± 20.7	n.s.	90.0 ± 12.5	87.3 ± 16.6	n.s.	91.0 ± 18.5	90.8 ± 19.0	n.s.
BMI (kg/m ²)	34.3 ± 8.1	33.0 ± 6.0	n.s.	32.0 ± 4.9	32.0 ± 5.2	n.s.	33.3 ± 6.9	32.5 ± 5.6	n.s.
Waist circumference (cm)	106.6 ± 18.1	106.6 ± 13.4	n.s.	105.3 ± 12.0	101.8 ± 13.0	n.s.	106.1 ± 15.6	104.2 ± 13.3	n.s.
Hip circumference (cm)	115.5 ± 15.9	114.0 ± 13.0	n.s.	111.7 ± 10.6	111.5 ± 12.9	n.s.	113.8 ± 13.9	112.7 ± 12.9	n.s.
WHR	0.92 ± 0.09	0.94 ± 0.08	n.s.	0.94 ± 0.07	0.92 ± 0.08	n.s.	0.93 ± 0.08	0.93 ± 0.08	n.s.
BIA—Body fat (%)	37.2 ± 10.3	35.3 ± 7.7	n.s.	32.6 ± 9.4	37.7 ± 7.7	n.s.	35.7 ± 1.01	36.6 ± 7.7	n.s.
Glycemia									
Fasting glucose (mg/dL)	87.6 ± 9.0	92.7 ± 10.3	n.s.	91.6 ± 10.4	89.8 ± 10.7	n.s.	89.3 ± 9.7	91.2 ± 10.5	n.s.
1-h glucose (mg/dL)	183.5 ± 32.3	206.6 ± 29.4	0.011	207.0 ± 29.8	197.5 ± 34.1	n.s.	193.5 ± 33.0	202.0 ± 32.0	n.s.
2-h glucose (mg/dL)	150.3 ± 14.2	164.8 ± 18.8	0.002	151.9 ± 12.1	159.4 ± 16.8	n.s. (p = 0.102)	151.0 ± 13.2	162.0 ± 17.9	0.001
Glucose AUC (mg/dL*min)	19,391.6 ± 2045.4	21,271.5 ± 2236.8	0.004	20,399.0 ± 2799.3	20,635.9 ± 2584.1	n.s.	19,828.2 ± 2410.1	20,950.4 ± 2426.8	0.020
Insulin Resistance and Beta-Cell Function									
Fasting insulin (mU/L)	9.0 ± 3.8	10.4 ± 6.3	n.s.	7.8 ± 3.6	9.2 ± 4.6	n.s.	8.5 ± 3.7	9.8 ± 5.5	n.s.
Fasting c-Peptide (µg/L)	1.7 ± 0.5	1.7 ± 0.8	n.s.	1.6 ± 0.8	1.6 ± 0.7	n.s.	1.6 ± 0.6	1.7 ± 0.7	n.s.
Cederholm	41.1 ± 10.3	35.4 ± 12.9	0.032	39.8 ± 15.1	36.7 ± 10.6	n.s.	40.5 ± 12.4	36.0 ± 11.7	n.s. (p = 0.052)
HOMA-beta	85.7 ± 39.6	80.9 ± 40.4	n.s.	62.0 ± 29.7	79.3 ± 35.7	n.s.	75.7 ± 37.2	8.1 ± 37.9	n.s.
NAFLD									
Fatty liver index	70 ± 32	72 ± 25	n.s.	71 ± 26	67 ± 26	n.s.	71 ± 29	70 ± 25	n.s.

Interventional changes of total energy, fat and fiber intake, body weight and physical activity were not significantly different between metabolic outcome groups (Table 2).

Table 2. Changes in lifestyle parameters during the one-year PREDIAS intervention; Mann–Whitney tests for comparison of NGR and non-NGR subgroups.

Lifestyle Changes over One Year	Full Cohort		
	NGR (<i>n</i> = 33)	No NGR (<i>n</i> = 98)	<i>p</i> -Value
Eating Behavior			
Change in body weight (kg)	−3.6 ± 5.1	−3.3 ± 5.7	n.s.
Change in energy intake (kcal)	−275 ± 547	−273 ± 474	n.s.
Change in fat intake (%)	−4.1 ± 7.4	−1.8 ± 6.4	n.s.
Change in dietary fiber intake (g)	0 ± 8	0 ± 8	n.s.
Change in supplemented fiber intake (g)	6 ± 9	7 ± 10	n.s.
Physical Activity			
Change in steps per day (n)	−278 ± 2692	629 ± 2865	n.s.

Interventional changes in waist circumference (as a surrogate for visceral fat) correlated with changes of the Cederholm index in the fiber group, and with both changes of the Cederholm index and fasting glucose in the total cohort. Changes in FLI correlated with changes of the Cederholm index in both groups and the full cohort as well as with 2 h glucose in the full cohort. Insulin secretion capacity (HOMA-beta) was the only metabolic variable not showing any linkage to changes in body fat depots in any study group nor the full cohort (Table 3A–C).

Table 3. Correlation of fold changes in body fat compartments and metabolic outcomes; (A): placebo group, (B): fiber group; (C): total cohort; Spearman correlations. Significant results are printed in bold; *: *p* < 0.05; **: *p* < 0.01; ***: *p* < 0.001.

(A)						
Variable	Change in Body fat _{BIA}		Change in Waist Circumference		Change in FLI	
	ρ	<i>p</i>	ρ	<i>p</i>	ρ	<i>p</i>
Change in fasting glucose	−0.081	0.559	0.224	0.068	0.104	0.405
Change in 2 h glucose	0.034	0.807	0.075	0.545	0.217	0.080
Change in Cederholm index	−0.171	0.221	−0.149	0.232	−0.320	0.009 **
Change in HOMA-beta	0.077	0.586	0.028	0.824	0.141	0.258
(B)						
Variable	Change in Body fat _{BIA}		Change in Waist Circumference		Change in FLI	
	ρ	<i>p</i>	ρ	<i>p</i>	ρ	<i>p</i>
Change in fasting glucose	0.159	0.265	0.223	0.077	0.089	0.487
Change in 2 h glucose	0.030	0.836	0.049	0.699	0.176	0.164
Change in Cederholm index	−0.150	0.293	−0.300	0.017 *	−0.489	<0.001 ***
Change in HOMA-beta	0.155	0.276	−0.185	0.143	−0.049	0.699
(C)						
Variable	Change in Body fat _{BIA}		Change in Waist Circumference		Change in FLI	
	ρ	<i>p</i>	ρ	<i>p</i>	ρ	<i>p</i>
Change in fasting glucose	0.038	0.700	0.233	0.007 **	0.104	0.241
Change in 2 h glucose	0.020	0.837	0.052	0.555	0.201	0.022 *
Change in Cederholm index	−0.144	0.145	−0.216	0.014 *	−0.403	<0.001 ***
Change in HOMA-beta	0.098	0.320	−0.065	0.465	0.057	0.523

In the multivariate logistic regression analysis, neither fasting glucose, liver fat content, insulin resistance nor insulin secretion were predictive markers for metabolic response, but

only 2 h glucose levels significantly predicted the response to lifestyle intervention within the total cohort (Table 4).

Table 4. Likelihood ratios for multivariate nominal logistic regression model for prediction of conversion to normal glucose regulation. Sex and Cederholm \times FLI were analyzed as categorical variables. Significant results are printed in bold; *: $p < 0.05$.

Variable	Placebo Group		Fiber Group		Total Cohort	
	Likelihood Ratio χ^2	p Value	Likelihood Ratio χ^2	p Value	Likelihood Ratio χ^2	p Value
Sex	0.062	0.803	0.100	0.751	0.133	0.715
Age	0.204	0.652	0.474	0.491	0.000	0.984
BMI	0.510	0.475	2.628	0.105	0.020	0.886
Waist circumference	0.014	0.907	2.545	0.111	0.327	0.567
Fasting glucose levels	0.782	0.377	0.233	0.629	0.033	0.856
2 h glucose levels	3.360	0.067	2.282	0.131	5.588	0.018 *
HOMA-beta	0.402	0.526	2.842	0.092	0.040	0.842
Cederholm index	0.089	0.765	0.474	0.491	0.073	0.787
Fatty liver index (FLI)	0.101	0.751	0.314	0.575	0.001	0.971
Cederholm \times FLI	0.794	0.373	0.371	0.543	0.103	0.748

Finally, we assessed if a classification of risk phenotypes according to insulin secretion and/or insulin-resistant fatty liver disease indicated different changes in 2 h glucose levels, when comparing the phenotypes. First, we classified all subjects in analogy to the TULIP study: subjects with insulin secretion capacity (HOMA-beta) below median and/or insulin-resistant NAFLD (insulin sensitivity (Cederholm index) below median and FLI > 60) were considered as high risk, and all others as low risk (model 1). As insulin resistance and fatty liver index (but not insulin secretion) correlated with changes in body fat and glycemia, we hypothesized that an insulin-resistant NAFLD might not be an independent risk factor. Therefore, we tested an additional classification where only insulin secretion failure—strongly reflected by 2 h glucose—was defined as a high-risk phenotype and all subjects with normal insulin secretion—including those with insulin-resistant NAFLD—were considered as low risk (model 2). ANCOVAs on the relative change of 2 h glucose levels (all models including sex, age and treatment group) did not show a significant difference between respective high- and low-risk groups (adjusted model 1: $p = 0.512$, adjusted model 2: $p = 0.358$), nor an interaction with sex and the treatment group (interaction model 1: $p = 0.142$; interaction model 2: $p = 0.146$).

4. Discussion

Our analysis is the first attempt to replicate the risk categorization of TULIP. Perhaps surprisingly, in our study, NAFLD—either with or without concomitant insulin resistance—did not qualify as a high-risk phenotype. Equally opposite to the results from TULIP, higher fasting glucose levels turned out to be neutral or even beneficial concerning metabolic success in OptiFit [24–29,44]. Nevertheless, we confirm a major finding of previous cohort and intervention studies: impaired insulin secretion capacity determines non-response to lifestyle intervention. This is reflected by the absence of correlations between the change in insulin secretion (HOMA-beta) with interventional changes in body fat depots. In support of this, higher levels of 2 h glucose—predominantly mirroring peripheral insulin resistance and/or failure in 2nd-phase insulin secretion—are a strong predictor for failure to achieve NGR in our trial [45,46].

According to previous large-scale RCTs on diabetes prevention with thousands of patients from Finland, the USA, China, Japan and India, respectively, lifestyle intervention is capable of reducing diabetes risk by up to 50% in the long-term perspective, to improve quality of life and to prevent late complications [4–7]. These studies further highlighted that the *metabolic* heterogeneity of patients results in *clinical* heterogeneity in interventional outcomes: not all subgroups of subjects achieve glycemic normalization, despite

sufficient compliance to treatment. While the existence of different risk types is a fact, the distinct definitions of those phenotypes are still disputed. The above-mentioned large intervention trials consistently showed that the IFG-IGT phenotype (bearing a higher risk for NAFLD than NFG-IGT) is especially responsive to a low-fat diet and increased physical activity [24–29].

IFG, either as an isolated feature or combined with glucose intolerance, is strongly connected to a weakened 1st-phase insulin secretion capacity [47,48]. Isolated glucose intolerance is identified as a risk factor for non-response [24–29], as 2 h glucose levels are reported to be major drivers of treatment failure [5]. IGT—be it isolated or combined with IFG—mirrors declining whole-body insulin sensitivity and reduced 2nd-phase insulin secretion, and bears a higher risk for progression, especially due to its tendency towards metabolic non-response [14–17].

The TULIP study pointed out that low insulin secretion capacity (defined by the 1st-phase insulin secretion marker “disposition index”) and insulin-resistant fatty liver are independent risk factors for lifestyle non-response [31]. Both beta-cell failure and (insulin-resistant) fatty liver have been considered as risk factors for disease progression in prediabetes cohorts *without* treatment; NAFLD was seen as a problematic state especially when combined with IFG [46,47,49]. *Intervention* studies soon confirmed and emphasized that beta-cell dysfunction and insulin resistance are indeed major players in counteracting the induction of metabolic improvements [50,51]. In our current analysis, insulin secretion was not connected to any glycemic or anthropometric response to lifestyle treatment, supporting the notion of a response-determining risk factor, despite a lack of significance in the logistic regression analysis. IGT cohorts such as OptiFiT predominantly include insulin-deficient subjects, possibly masking the strong disadvantage of this metabolic feature in comparison to underrepresented subjects with preserved secretion capacity. However, it seems logical that patients with early beta-cell dysfunction as a potentially genetic feature (as it is already present in prediabetes) cannot improve the metabolism despite losing weight and improving diet quality.

Neither insulin resistance, NAFLD nor their combination predicted non-response in our analysis. Reductions in waist circumference and FLI were correlated with improvements in the Cederholm index. Despite being risk factors for T2DM onset under *observational* conditions, it seems that these factors can be at least partially ameliorated by lifestyle measures, even in a high-risk cohort such as OptiFiT.

A possible explanation for the inconsistencies between OptiFiT and TULIP may be found in their cohort structure. OptiFiT exclusively recruited subjects with IGT (isolated and combined with IFG), while TULIP also contained subjects with isolated IFG. The latter usually makes up about 30–40% of all prediabetes cases. Usually, patients with isolated IFG show higher levels of liver fat than subjects with isolated IGT [13]. Surprisingly, this was not the case in the TULIP cohort [52], while OptiFiT replicated this difference between IFG-IGT and isolated IGT [28,44].

In both TULIP and OptiFiT, the insulin secretion deficit was defined by the median of the respective secretion index (disposition index, HOMA-beta), i.e., in both studies, 50% of the cohort were considered insulin-deficient. In TULIP, only 10% (12/120) had an insulin-resistant NAFLD with normal insulin secretion [31], while in OptiFiT, 29% (38/131) showed this phenotype. Thus, the high-risk phenotype in TULIP—rather than in OptiFiT—is strongly dominated by patients with secretion deficit (with or without additional insulin-resistant NAFLD). Earlier reports on the regional distribution of prediabetes subtypes within Germany support the plausibility of these differences [53].

By having a sufficiently large proportion of patients with insulin-resistant NAFLD, OptiFiT specifically might be able to demonstrate that this phenotype is not resistant to lifestyle intervention. This does not contradict cohort studies showing the independent contribution of NAFLD to diabetes risk, as they assess “natural progression” rather than *treatment* responsiveness [54,55].

Even though we cannot replicate the TULIP finding on the high-risk potential of an insulin-resistant NAFLD, our current analysis of OptiFiT supports the findings of DPP and DREAM, highlighting that the response to interventions mainly depends on the glycemic state itself. Higher levels of 2 h glucose predict treatment failure, while isolated or the additional impairment of fasting glucose increases the chances for treatment success [23–27]. Similarly, IFG-IGT patients in OptiFiT were characterized by higher post-challenge glucose levels than NFG-IGT subjects, but they had a better outcome. The fiber supplementation seemed to compensate for the additional metabolic disadvantage, resulting in a significant interaction effect (IFG × treatment) [28,44].

Previous prediabetes studies had proposed to use 1 h glucose levels as an additional or even superior risk parameter for diabetes progression [56]. Our data imply that under interventional rather than observational conditions, this diagnostic superiority is absent.

In both TULIP and OptiFiT, all subjects were motivated to increase their physical activity, to reduce fat intake and to increase their fiber intake from daily food sources. Apart from fiber intake, any other lifestyle aspect might have affected the metabolic outcome: weight loss, reduction in fat intake and increased physical activity [57]. Responders and non-responders did not differ in these intervention-induced changes, ruling out further explanatory factors for non-response. Compliance was not a relevant effect modulator. However, poor compliance to fiber-rich diets has been consistently reported from large diabetes prevention trials [58] and in OptiFiT [32], underlining our focus on insoluble cereal fiber in all efforts (natural food sources, fortification and supplementation) to reduce diabetes incidence [59,60]. The limited compliance to the recommendation of fiber-rich food might explain the impact of supplementation: in the placebo group, NGR and non-NGR subjects differed in various glycemic baseline parameters. In the fiber group, 2 h glucose at baseline was the only (trend-wise) discriminant between subjects achieving NGR or non-NGR. On the other hand, in the fiber group, improvements in NAFLD and visceral fat amount were more strongly linked to improved insulin sensitivity compared to placebo. This mirrors the accentuated effectiveness of the fiber treatment in IFG-IGT and/or obese subjects as previously shown [28,44].

There are, however, some limitations to our analysis. Compared to other large lifestyle RCTs, OptiFiT was a rather small trial, limiting power for comparisons. Furthermore, male subjects were underrepresented. Nevertheless, our cohort was of a similar size as the prediabetes subgroup of TULIP and the intervention entailed a 30% low-fat diet and exercise recommendation of similar duration. These properties provided sufficient comparability [31].

The blood sampling protocol for OptiFiT was very restrictive due to budget reasons. By forfeiting 30' sampling for insulin levels, indices for post-challenge insulin secretion (e.g., disposition index) and several insulin sensitivity indices (such as Matsuda) could not be assessed. We therefore used the Cederholm index to assess insulin sensitivity, which provided predictive properties comparable to the Matsuda [61–63]. HOMA-beta as an alternative to the disposition index is commonly used as a cross-sectional and prospective surrogate of insulin secretion [11,64–66].

Additionally, liver fat measurements were only available in a small subgroup which required the use of the FLI to describe the NAFLD status at baseline. For this purpose alone, the FLI is sufficiently reliable and commonly used as a diabetes predictor in epidemiology [18–22,44]. The FLI provides a similar predictive power compared to sonography [67,68]. Changes in liver fat due to a low-fat diet can be described on the basis of changes in FLI [69].

We experienced a one-year drop-out rate of 24%. This is comparable to the 9-month TULIP and should not explain differences in the results between TULIP and OptiFiT [31]. In OptiFiT, the onset of T2DM was a drop-out criterion, but only one case did not take part in the one-year visit. Drop-outs similarly limit the prediction quality of both the TULIP and OptiFiT models.

By using 4-day food records, we were able to evaluate dietary compliance and could outrule a considerable misinterpretation by under-/overreporting or under-/overeating in the absence of valid biomarkers for dietary protocol adherence. The parallel use of pedometers and EPAQ-2 questionnaires assured the analysis of physical activity based on both objective and subjective parameters. Compliance to recommendations for both diet and physical activity was moderate, but comparable between intervention groups, responders and non-responders, as well as TULIP and OptiFiT. The well-accepted OptiFiT fiber supplement provided the unique chance to significantly raise fiber intake.

In the same way as the TULIP analysis, our assessment included sex as a potential effect modulator, but was not powered for a sex-stratified approach. The prevalence of NAFLD and prediabetes subtypes differed between sexes, but as the statistical procedure clearly split up these phenotypes, the modulating effect of sex was minimized [70].

5. Conclusions

In summary, insulin resistance, measures of liver fat content and the insulin-resistant NAFLD did not appear as factors modulating the risk for non-response and might be considered as both therapeutic targets and predictors for successful lifestyle treatment.

We further replicated previous findings on glycemic predictors for the metabolic non-response to lifestyle treatment. Fasting glucose and—more consistently for different treatments—post-challenge 2 h glucose determined the chance to achieve NGR or NGT. Insulin secretion capacity did not change in parallel to measures of excess fat depots. Thus, impaired insulin secretion seems to consistently represent a major obstacle with respect to lifestyle-dependent metabolic improvements.

We warrant detailed subgroup analyses for other non-pharmaceutical prevention trials will clearly determine the risk factors for T2DM progression despite sufficient compliance.

Author Contributions: S.K. wrote the paper; C.H., C.G. and U.D. conducted the experiments by dietary consultation, and collected and interpreted referring data; S.K. and M.K. performed all medical examinations and the medical supervision for the participants and collected and interpreted referring data; S.K., N.M.T.M., C.H. and M.A.O. performed the statistical analysis; C.G., A.M.A., M.O.W. and A.F.H.P. designed the study; all authors read and revised the manuscript, contributed to discussion and approved the final version of this paper; S.K. is responsible for the integrity of the work as a whole and serves as guarantor of this work. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: OptiFiT, the Optimal Fiber Trial, was registered at clinicaltrials.gov: NCT01681173 (first registered on 7 September 2012). The study protocol was approved by the ethics committee of the University of Potsdam as well as the ethics committee of the Charité, and all individuals gave written informed consent. OptiFiT was conducted in accordance with the Declaration of Helsinki and GCP-ICH.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data sets are available by request to the corresponding author.

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Abbreviations

AUC	area under the curve
BIA	bioelectric impedance analysis
FLI	fatty liver index
HIC	hepatic insulin clearance
HOMA _{IR}	homeostasis model assessment insulin resistance index
HOMA-beta	homeostasis model assessment insulin for beta cell function
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
ISI _{ffa}	insulin sensitivity index of blood free fatty acids
NAFLD	nonalcoholic fatty liver disease
NFG	normal fasting glucose
NGR	normal glucose regulation
NGT	normal glucose tolerance
OptiFiT	Optimal Fiber Trial for diabetes prevention
OGTT	oral glucose tolerance test
T2DM	type 2 diabetes mellitus

Appendix A

Table A1. Characteristics of responders and non-responders (NGT) at study entry; Mann–Whitney tests for comparison of NGT and non-NGT subgroups.

Characteristics of Participants at Study Entry	Placebo Arm			Fiber Arm			Full Cohort		
	NGT (n = 23)	No NGT (n = 44)	p-Value	NGT (n = 23)	No NGT (n = 41)	p-Value	NGT (n = 46)	No NGT (n = 85)	p-Value
Cohort Structure									
Age	61 ± 10	60 ± 9	n.s.	56 ± 10	62 ± 8	0.018	58 ± 10	61 ± 9	n.s.
Sex	57%	50%	n.s.	78%	68%	n.s.	67%	59%	n.s.
Anthropometry									
Weight (kg)	92.2 ± 21.7	94.5 ± 20.9	n.s.	91.1 ± 13.1	86.1 ± 16.9	n.s.	91.7 ± 17.7	90.4 ± 19.4	n.s.
BMI (kg/m ²)	33.7 ± 7.7	33.2 ± 6.0	n.s.	33.0 ± 4.7	31.5 ± 5.3	n.s.	33.3 ± 6.3	32.3 ± 5.7	n.s.
Waist circumference (cm)	106.8 ± 18.2	106.5 ± 12.8	n.s.	105.8 ± 12.0	100.8 ± 13.0	n.s.	106.3 ± 15.2	103.8 ± 13.1	n.s.
Hip circumference (cm)	115.1 ± 15.9	114.0 ± 12.7	n.s.	114.6 ± 11.3	109.8 ± 12.8	n.s.	114.8 ± 13.6	112.0 ± 12.8	n.s.
WHR	0.93 ± 0.08	0.94 ± 0.09	n.s.	0.92 ± 0.07	0.92 ± 0.09	n.s.	0.93 ± 0.07	0.93 ± 0.09	n.s.
BIA—Body fat (%)	36.8 ± 10.2	35.4 ± 7.4	n.s.	37.5 ± 8.7	36.7 ± 8.0	n.s.	37.1 ± 9.4	36.0 ± 7.7	n.s.
Glycemia									
Fasting glucose (mg/dL)	87.7 ± 9.2	93.1 ± 10.2	n.s. (p = 0.053)	91.7 ± 9.2	89.3 ± 11.3	n.s.	89.7 ± 9.3	91.3 ± 10.8	n.s.
1 h glucose (mg/dL)	189.8 ± 34.8	205.4 ± 29.0	n.s. (p = 0.069)	201.7 ± 28.6	189.4 ± 35.8	n.s.	195.7 ± 32.1	202.0 ± 32.5	n.s.
2 h glucose (mg/dL)	149.4 ± 13.2	166.6 ± 18.5	<0.001	153.0 ± 12.9	160.4 ± 17.3	n.s. (p = 0.078)	151.2 ± 13.0	163.6 ± 18.1	<0.001
Glucose AUC (mg/dL*min)	19,777.6 ± 2261.9	21,257.9 ± 2225.2	0.018	20,288.8 ± 2430.9	20,752.8 ± 2721.0	n.s.	20,039.2 ± 2336.1	21,017.7 ± 2470.9	0.027
Insulin Resistance and Beta-Cell Function									
Fasting insulin (mU/L)	8.7 ± 4.0	10.7 ± 6.3	n.s.	8.7 ± 3.8	9.0 ± 4.7	n.s.	8.7 ± 3.9	9.9 ± 5.6	n.s.
Fasting c-Peptide (µg/L)	1.6 ± 0.6	1.7 ± 0.7	n.s.	1.7 ± 0.8	1.6 ± 0.7	n.s.	1.7 ± 0.7	1.6 ± 0.7	n.s.
Cederholm	40.8 ± 10.7	35.0 ± 12.9	0.027	38.6 ± 12.1	36.7 ± 11.6	n.s.	39.7 ± 11.4	35.8 ± 12.2	0.034
HOMA-beta	79.1 ± 39.9	83.9 ± 40.3	n.s.	73.1 ± 30.8	76.9 ± 37.4	n.s. (p = 0.093)	76.1 ± 35.4	80.5 ± 38.9	n.s.
NAFLD									
Fatty liver index	70 ± 32	72 ± 24	n.s.	73 ± 24	65 ± 27	n.s.	72 ± 28	69 ± 26	n.s.

References

1. Meigs, J.B.; Cupples, L.A.; Wilson, P.W. Parental transmission of type 2 diabetes: The Framingham Offspring Study. *Diabetes* **2000**, *49*, 2201–2207. [[CrossRef](#)] [[PubMed](#)]
2. Hu, F.B.; Sigal, R.J.; Rich-Edwards, J.W.; Colditz, G.A.; Solomon, C.G.; Willett, W.C.; Speizer, F.E.; Manson, J.E. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: A prospective study. *JAMA* **1999**, *282*, 1433–1439. [[CrossRef](#)] [[PubMed](#)]
3. Nolan, C.J.; Damm, P.; Prentki, M. Type 2 diabetes across generations: From pathophysiology to prevention and management. *Lancet* **2011**, *378*, 169–181. [[CrossRef](#)]
4. Pan, X.R.; Li, G.W.; Hu, Y.H.; Wang, J.X.; Yang, W.Y.; An, Z.X.; Hu, Z.X.; Lin, J.; Xiao, J.Z.; Cao, H.B.; et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* **1997**, *20*, 537–544. [[CrossRef](#)]
5. Ramachandran, A.; Snehalatha, C.; Mary, S.; Mukesh, B.; Bhaskar, A.D.; Vijay, V.; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* **2006**, *49*, 289–297. [[CrossRef](#)]
6. Knowler, W.C.; Barrett-Connor, E.; Fowler, S.E.; Hamman, R.F.; Lachin, J.M.; Walker, E.A.; Nathan, D.M.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **2002**, *346*, 393–403.
7. Tuomilehto, J.; Lindstrom, J.; Eriksson, J.G.; Valle, T.T.; Hämäläinen, H.; Ilanne-Parikka, P.; Keinänen-Kiukaanniemi, S.; Laakso, M.; Louheranta, A.; Rastas, M.; et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* **2001**, *344*, 1343–1350. [[CrossRef](#)]
8. Weickert, M.O. Nutritional modulation of insulin resistance. *Scientifica* **2012**, *2012*, 424780. [[CrossRef](#)]
9. Ley, S.H.; Hamdy, O.; Mohan, V.; Hu, F.B. Prevention and management of type 2 diabetes: Dietary components and nutritional strategies. *Lancet* **2014**, *383*, 1999–2007. [[CrossRef](#)]
10. Kulzer, B.; Hermanns, N.; Gorges, D.; Schwarz, P.; Haak, T. Prevention of diabetes self-management program (PREDIAS): Effects on weight, metabolic risk factors, and behavioral outcomes. *Diabetes Care* **2009**, *32*, 1143–1146. [[CrossRef](#)]
11. Ahlqvist, E.; Storm, P.; Käräjämäki, A.; Martinell, M.; Dorkhan, M.; Carlsson, A.; Vikman, P.; Prasad, R.B.; Aly, D.M.; Almgren, P.; et al. Novel subgroups of adult-onset diabetes and their association with outcomes: A data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol.* **2018**, *6*, 361–369. [[CrossRef](#)]
12. Stidsen, J.V.; Henriksen, J.E.; Olsen, M.H.; Thomsen, R.W.; Nielsen, J.S.; Rungby, J.; Ulrichsen, S.P.; Berencsi, K.; Kahlert, J.A.; Friberg, S.G.; et al. Pathophysiology-based phenotyping in type 2 diabetes: A clinical classification tool. *Diabetes Metab. Res. Rev.* **2018**, *34*, e3005. [[CrossRef](#)] [[PubMed](#)]
13. Rückert, I.M.; Heier, M.; Rathmann, W.; Baumeister, S.E.; Döring, A.; Meisinger, C. Association between markers of fatty liver disease and impaired glucose regulation in men and women from the general population: The KORA-F4-study. *PLoS ONE* **2011**, *6*, e22932. [[CrossRef](#)] [[PubMed](#)]
14. Janghorbani, M.; Amini, M. Comparison of fasting glucose with post-load glucose values and glycated hemoglobin for prediction of type 2 diabetes: The Isfahan diabetes prevention study. *Rev. Diabet. Stud.* **2009**, *6*, 117–123. [[CrossRef](#)] [[PubMed](#)]
15. Pallardo, L.F.; Herranz, L.; Martin-Vaquero, P.; Garcia-Ingelmo, T.; Grande, C.; Jañez, M. Impaired fasting glucose and impaired glucose tolerance in women with prior gestational diabetes are associated with a different cardiovascular profile. *Diabetes Care* **2003**, *26*, 2318–2322. [[CrossRef](#)] [[PubMed](#)]
16. Ghachem, A.; Brochu, M.; Dionne, I.J. Differential clusters of modifiable risk factors for impaired fasting glucose versus impaired glucose tolerance in adults 50 years of age and older. *Ther. Adv. Chronic Dis.* **2019**, *10*, 2040622319854239. [[CrossRef](#)]
17. Kowall, B.; Rathmann, W.; Bongaerts, B.; Kuss, O.; Stang, A.; Roden, M.; Herder, C.; Koenig, W.; Huth, C.; Heier, M.; et al. Incidence Rates of Type 2 Diabetes in People with Impaired Fasting Glucose (ADA vs. WHO Criteria) and Impaired Glucose Tolerance: Results from an Older Population (KORA S4/F4/FF4 Study). *Diabetes Care* **2019**, *42*, e18–e20. [[CrossRef](#)]
18. Mantovani, A.; Petracca, G.; Beatrice, G.; Tilg, H.; Byrne, C.D.; Targher, G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: An updated meta-analysis of 501,022 adult individuals. *Gut* **2021**, *70*, 962–969. [[CrossRef](#)]
19. Jäger, S.; Jacobs, S.; Kröger, J.; Stefan, N.; Fritsche, A.; Weikert, C.; Boeing, H.; Schulze, M.B. Association between the Fatty Liver Index and Risk of Type 2 Diabetes in the EPIC-Potsdam Study. *PLoS ONE* **2015**, *10*, e0124749. [[CrossRef](#)]
20. García-Escobar, E.; Valdés, S.; Soriguer, F.; Vendrell, J.; Urrutia-Etxebarria, I.M.; Maldonado-Araque, C.; Ortega, E.; Ocón, P.; Montanya, E.; Menéndez, E.; et al. Fatty liver index as a predictor for type 2 diabetes in subjects with normoglycemia in a nationwide cohort study. *Sci. Rep.* **2021**, *11*, 16453. [[CrossRef](#)]
21. Chung, G.E.; Cho, E.J.; Yoon, J.W.; Yoo, J.-J.; Chang, Y.; Cho, Y.; Park, S.-H.; Han, K.; Shin, D.W.; Yu, S.J. Nonalcoholic fatty liver disease increases the risk of diabetes in young adults: A nationwide population-based study in Korea. *Metabolism* **2021**, *123*, 154866. [[CrossRef](#)] [[PubMed](#)]
22. Cuthbertson, D.J.; Koskinen, J.; Brown, E.; Magnussen, C.G.; Hutri-Kähönen, N.; Sabin, M.; Tossavainen, P.; Jokinen, E.; Laitinen, T.; Viikari, J.; et al. Fatty liver index predicts incident risk of prediabetes, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). *Ann. Med.* **2021**, *53*, 1256–1264. [[CrossRef](#)]

23. Hulman, A.; Gujral, U.P.; Narayan, K.M.V.; Pradeepa, R.; Mohan, D.; Anjana, R.M.; Mohan, V.; Færch, K.; Witte, D.R. Glucose patterns during the OGTT and risk of future diabetes in an urban Indian population: The CARRS study. *Diabetes Res. Clin. Pract.* **2017**, *126*, 192–197. [[CrossRef](#)]
24. Diabetes Prevention Program Research Group. Long-Term Effects of Metformin on Diabetes Prevention: Identification of Subgroups That Benefited Most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care* **2019**, *42*, 601–608. [[CrossRef](#)]
25. DREAM (Diabetes REduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: A randomised controlled trial. *Lancet* **2006**, *368*, 1096–1105. [[CrossRef](#)]
26. Hjorth, M.F.; Zohar, Y.; Hill, J.O.; Astrup, A. Personalized Dietary Management of Overweight and Obesity Based on Measures of Insulin and Glucose. *Annu. Rev. Nutr.* **2018**, *38*, 245–272. [[CrossRef](#)] [[PubMed](#)]
27. Hjorth, M.F.; Bray, G.A.; Zohar, Y.; Urban, L.; Miketinas, D.C.; Williamson, D.A.; Ryan, D.H.; Rood, J.; Champagne, C.M.; Sacks, F.M.; et al. Pretreatment Fasting Glucose and Insulin as Determinants of Weight Loss on Diets Varying in Macronutrients and Dietary Fibers—The POUNDS LOST Study. *Nutrients* **2019**, *11*, 586. [[CrossRef](#)]
28. Kabisch, S.; Meyer, N.M.T.; Honsek, C.; Gerbracht, C.; Dambeck, U.; Kemper, M.; Osterhoff, M.A.; Birkenfeld, A.L.; Arafat, A.M.; Hjorth, M.F.; et al. Fasting Glucose State Determines Metabolic Response to Supplementation with Insoluble Cereal Fibre: A Secondary Analysis of the Optimal Fibre Trial (OptiFiT). *Nutrients* **2019**, *11*, 2385. [[CrossRef](#)]
29. Saaristo, T.; Moilanen, L.; Korpi-Hyövälti, E.; Vanhala, M.; Saltevo, J.; Niskanen, L.; Jokelainen, J.; Peltonen, M.; Oksa, H.; Tuomilehto, J.; et al. Lifestyle intervention for prevention of type 2 diabetes in primary health care: One-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D). *Diabetes Care* **2010**, *33*, 2146–2151. [[CrossRef](#)]
30. Sakane, N.; Kotani, K.; Suganuma, A.; Takahashi, K.; Sato, J.; Suzuki, S.; Izumi, K.; Kato, M.; Noda, M.; Nirengi, S.; et al. Effects of obesity, metabolic syndrome, and non-alcoholic or alcoholic elevated liver enzymes on incidence of diabetes following lifestyle intervention: A subanalysis of the J-DOIT1. *J. Occup. Health* **2020**, *62*, e12109. [[CrossRef](#)]
31. Stefan, N.; Staiger, H.; Wagner, R.; Machann, J.; Schick, F.; Häring, H.-U.; Fritsche, A. A high-risk phenotype associates with reduced improvement in glycaemia during a lifestyle intervention in prediabetes. *Diabetologia* **2015**, *58*, 2877–2884. [[CrossRef](#)] [[PubMed](#)]
32. Honsek, C.; Kabisch, S.; Kemper, M.; Gerbracht, C.; Arafat, A.M.; Birkenfeld, A.L.; Dambeck, U.; Osterhoff, M.A.; Weickert, M.O.; Pfeiffer, A.F.H. Fibre supplementation for the prevention of type 2 diabetes and improvement of glucose metabolism: The randomised controlled Optimal Fibre Trial (OptiFiT). *Diabetologia* **2018**, *61*, 1295–1305. [[CrossRef](#)] [[PubMed](#)]
33. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* **2001**, *285*, 2486–2497. [[CrossRef](#)]
34. Lindstrom, J.; Neumann, A.; Sheppard, K.E.; Gilis-Januszewska, A.; Greaves, C.J.; Handke, U.; Pajunen, P.; Puhl, S.; Pölonen, A.; Rissanen, A.; et al. Take action to prevent diabetes—The IMAGE toolkit for the prevention of type 2 diabetes in Europe. *Horm. Metab. Res.* **2010**, *42* (Suppl. S1), S37–S55. [[CrossRef](#)] [[PubMed](#)]
35. Wareham, N.J.; Jakes, R.W.; Rennie, K.L.; Mitchell, J.; Hennings, S.; Day, N.E. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. *Int. J. Epidemiol.* **2002**, *31*, 168–174. [[CrossRef](#)] [[PubMed](#)]
36. Hartmann, B.M.; Vasquez-Caicedo, A.L.; Bell, S.; Krems, C.; Brombach, C. The German nutrient database: Basis for analysis of the nutritional status of the German Population. *J. Food Comp. Anal.* **2008**, *21*, 115–118. [[CrossRef](#)]
37. Machann, J.; Thamer, C.; Schnoedt, B.; Stefan, N.; Häring, H.-U.; Claussen, C.D.; Fritsche, A.; Schick, F. Hepatic lipid accumulation in healthy subjects: A comparative study using spectral fat-selective MRI and volume-localized 1H-MR spectroscopy. *Magn. Reson. Med.* **2006**, *55*, 913–917. [[CrossRef](#)]
38. Retnakaran, R.; Shen, S.; Hanley, A.J.; Vuksan, V.; Hamilton, J.K.; Zinman, B. Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test. *Obesity* **2008**, *16*, 1901–1907. [[CrossRef](#)]
39. Matsuda, M.; DeFronzo, R.A. Insulin sensitivity indices obtained from oral glucose tolerance testing: Comparison with the euglycemic insulin clamp. *Diabetes Care* **1999**, *22*, 1462–1470. [[CrossRef](#)]
40. Kabisch, S.; Honsek, C.; Kemper, M.; Gerbracht, C.; Meyer, N.T.M.; Arafat, A.M.; Birkenfeld, A.L.; Machann, J.; Dambeck, U.; Osterhoff, M.A.; et al. Effects of Insoluble Cereal Fibre on Body Fat Distribution in the Optimal Fibre Trial (OptiFiT). *Mol. Nutr. Food Res.* **2021**, *65*, 2000991. [[CrossRef](#)]
41. Cederholm, J.; Wibell, L. Insulin release and peripheral sensitivity at the oral glucose tolerance test. *Diabetes Res. Clin. Pract.* **1990**, *10*, 167–175. [[CrossRef](#)]
42. Matthews, D.R.; Hosker, J.P.; Rudenski, A.S.; Naylor, B.A.; Treacher, D.F.; Turner, R.C. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **1985**, *28*, 412–419. [[CrossRef](#)] [[PubMed](#)]
43. Bedogni, G.; Bellentani, S.; Miglioli, L.; Masutti, F.; Passalacqua, M.; Castiglione, A.; Tiribelli, C. The Fatty Liver Index: A simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol.* **2006**, *6*, 33. [[CrossRef](#)]
44. Kabisch, S.; Meyer, N.M.T.; Honsek, C.; Gerbracht, C.; Dambeck, U.; Kemper, M.; Osterhoff, M.A.; Birkenfeld, A.L.; Arafat, A.M.; Weickert, M.O.; et al. Obesity Does Not Modulate the Glycometabolic Benefit of Insoluble Cereal Fibre in Subjects with Prediabetes—A Stratified Post Hoc Analysis of the Optimal Fibre Trial (OptiFiT). *Nutrients* **2019**, *11*, 2726. [[CrossRef](#)] [[PubMed](#)]

45. Perreault, L.; Kahn, S.E.; Christophi, C.A.; Knowler, W.C.; Hamman, R.F.; Diabetes Prevention Program Research Group. Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. *Diabetes Care* **2009**, *32*, 1583–1588. [[CrossRef](#)]
46. Kitabchi, A.E.; Tempresa, M.; Knowler, W.C.; Kahn, S.E.; Fowler, S.E.; Haffner, S.M.; Andres, R.; Saudek, C.; Edelstein, S.L.; Arakaki, R. Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: Effects of lifestyle intervention and metformin. *Diabetes* **2005**, *54*, 2404–2414.
47. Kanat, M.; Norton, L.; Winnier, D.; Jenkinson, C.; DeFronzo, R.A.; Abdul-Ghani, M.A. Impaired early—But not late-phase insulin secretion in subjects with impaired fasting glucose. *Acta Diabetol.* **2011**, *48*, 209–217. [[CrossRef](#)]
48. Sathananthan, A.; Man, C.D.; Zinsmeister, A.R.; Camilleri, M.; Rodeheffer, R.J.; Toffolo, G.; Cobelli, C.; Rizza, R.A.; Vella, A. A concerted decline in insulin secretion and action occurs across the spectrum of fasting and postchallenge glucose concentrations. *Clin. Endocrinol.* **2012**, *76*, 212–219. [[CrossRef](#)]
49. Bae, J.C.; Rhee, E.J.; Lee, W.Y.; Park, S.E.; Park, C.Y.; Oh, K.W.; Park, S.W.; Kim, S.W. Combined effect of nonalcoholic fatty liver disease and impaired fasting glucose on the development of type 2 diabetes: A 4-year retrospective longitudinal study. *Diabetes Care* **2011**, *34*, 727–729. [[CrossRef](#)]
50. Li, G.; Hu, Y.; Yang, W.; Jiang, Y.; Wang, J.; Xiao, J.; Hu, Z.; Pan, X.; Howard, B.V.; Bennett, P.H. Effects of insulin resistance and insulin secretion on the efficacy of interventions to retard development of type 2 diabetes mellitus: The DA Qing IGT and Diabetes Study. *Diabetes Res. Clin. Pract.* **2002**, *58*, 193–200. [[CrossRef](#)]
51. Wang, Q.; Jokelainen, J.; Auvinen, J.; Puukka, K.; Keinänen-Kiukaanniemi, S.; Järvelin, M.-R.; Kettunen, J.; Mäkinen, V.-P.; Ala-Korpela, M. Insulin resistance and systemic metabolic changes in oral glucose tolerance test in 5340 individuals: An interventional study. *BMC Med.* **2019**, *17*, 217. [[CrossRef](#)] [[PubMed](#)]
52. Kantartzis, K.; Machann, J.; Schick, F.; Fritsche, A.; Häring, H.U.; Stefan, N. The impact of liver fat vs. visceral fat in determining categories of prediabetes. *Diabetologia* **2010**, *53*, 882–889. [[CrossRef](#)] [[PubMed](#)]
53. Tamayo, T.; Schipf, S.; Meisinger, C.; Schunk, M.; Maier, W.; Herder, C.; Roden, M.; Nauck, M.; Peters, A.; Völzke, H.; et al. Regional differences of undiagnosed type 2 diabetes and prediabetes prevalence are not explained by known risk factors. *PLoS ONE* **2014**, *9*, e113154.
54. Sinn, D.H.; Kang, D.; Cho, S.J.; Paik, S.W.; Guallar, E.; Cho, J.; Gwak, G.-Y. Lean non-alcoholic fatty liver disease and development of diabetes: A cohort study. *Eur. J. Endocrinol.* **2019**, *181*, 185–192. [[CrossRef](#)] [[PubMed](#)]
55. Li, W.-D.; Fu, K.-F.; Li, G.-M.; Lian, Y.-S.; Ren, A.-M.; Chen, Y.-J.; Xia, J.-R. Comparison of effects of obesity and non-alcoholic fatty liver disease on incidence of type 2 diabetes mellitus. *World J. Gastroenterol.* **2015**, *21*, 9607–9613. [[CrossRef](#)]
56. Bergman, M.; Jagannathan, R.; Buyschaert, M.; Pareek, M.; Olsen, M.H.; Nilsson, P.M.; Medina, J.L.; Roth, J.; Chetrit, A.; Groop, L.; et al. Lessons learned from the 1-hour post-load glucose level during OGTT: Current screening recommendations for dysglycaemia should be revised. *Diabetes Metab. Res. Rev.* **2018**, *34*, e2992. [[CrossRef](#)]
57. Jeon, C.Y.; Lokken, R.P.; Hu, F.B.; van Dam, R.M. Physical activity of moderate intensity and risk of type 2 diabetes: A systematic review. *Diabetes Care* **2007**, *30*, 744–752. [[CrossRef](#)]
58. Lindstrom, J.; Ilanne-Parikka, P.; Peltonen, M.; Aunola, S.; Eriksson, J.G.; Hemiö, K.; Hämäläinen, H.; Härkönen, P.; Keinänen-Kiukaanniemi, S.; Laakso, M.; et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: Follow-up of the Finnish Diabetes Prevention Study. *Lancet* **2006**, *368*, 1673–1679. [[CrossRef](#)]
59. Weickert, M.O.; Pfeiffer, A.F. Metabolic effects of dietary fiber consumption and prevention of diabetes. *J. Nutr.* **2008**, *138*, 439–442. [[CrossRef](#)]
60. Weickert, M.O.; Pfeiffer, A.F.H. Impact of Dietary Fiber Consumption on Insulin Resistance and the Prevention of Type 2 Diabetes. *J. Nutr.* **2018**, *148*, 7–12. [[CrossRef](#)]
61. Cockcroft, E.J.; Williams, C.A.; Jackman, S.R.; Armstrong, N.; Barker, A.R. Agreement and Reliability of Fasted and Oral Glucose Tolerance Test-Derived Indices of Insulin Sensitivity and Beta Cell Function in Boys. *Int. J. Sports Med.* **2017**, *38*, 411–417. [[CrossRef](#)] [[PubMed](#)]
62. Zethelius, B.; Cederholm, J. Comparison between indexes of insulin resistance for risk prediction of cardiovascular diseases or development of diabetes. *Diabetes Res. Clin. Pract.* **2015**, *110*, 183–192. [[CrossRef](#)]
63. Haeckel, R.; Raber, R.; Wosniok, W. Comparability of indices for insulin resistance and insulin secretion determined during oral glucose tolerance tests. *Clin. Chem. Lab. Med.* **2006**, *44*, 817–823. [[CrossRef](#)] [[PubMed](#)]
64. Reaven, G.M. Insulin secretory function in type 2 diabetes: Does it matter how you measure it? *J. Diabetes* **2009**, *1*, 142–150. [[CrossRef](#)] [[PubMed](#)]
65. Zaharia, O.P.; Strassburger, K.; Strom, A.; Böhnhof, G.J.; Karusheva, Y.; Antoniou, S.; Bódis, K.; Markgraf, D.F.; Burkart, V.; Müssig, K.; et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: A 5-year follow-up study. *Lancet Diabetes Endocrinol.* **2019**, *7*, 684–694. [[CrossRef](#)]
66. Kahn, S.E.; Haffner, S.M.; Heise, M.A.; Herman, W.H.; Holman, R.R.; Jones, N.P.; Kravitz, B.G.; Lachin, J.M.; O'Neill, M.C.; Zinman, B.; et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* **2006**, *355*, 2427–2443. [[CrossRef](#)]
67. Ballestri, S.; Mantovani, A.; Byrne, C.D.; Lonardo, A.; Targher, G. Diagnostic accuracy of ultrasonography for the detection of hepatic steatosis: An updated meta-analysis of observational studies. *Metab. Target Organ Damage* **2021**, *1*, 7. [[CrossRef](#)]

68. Lonardo, A.; Ballestri, S.; Bedogni, G.; Bellentani, S.; Tiribelli, C. The Fatty liver Index (FLI) 15 years later: A reappraisal. *Metab. Target Organ Damage* **2021**, *1*, 10. [[CrossRef](#)]
69. Kabisch, S.; Bäther, S.; Dambeck, U.; Kemper, M.; Gerbracht, C.; Honsek, C.; Sachno, A.; Pfeiffer, A.F.H. Liver Fat Scores Moderately Reflect Interventional Changes in Liver Fat Content by a Low-Fat Diet but Not by a Low-Carb Diet. *Nutrients* **2018**, *10*, 157. [[CrossRef](#)]
70. Mauvais-Jarvis, F.; Merz, N.B.; Barnes, P.J.; Brinton, R.D.; Carrero, J.J.; DeMeo, D.L.; De Vries, G.J.; Epperson, C.N.; Govindan, R.; Klein, S.L.; et al. Sex and gender: Modifiers of health, disease, and medicine. *Lancet* **2020**, *396*, 565–582. [[CrossRef](#)]