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## **Research: Educational and psychological aspects**

# **Patient-reported outcomes after 10-year follow-up of intensive, multifactorial treatment in individuals with screen-detected type 2 diabetes: the ADDITION-Europe trial**

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### **What's new?**

- The burden of diabetes and its treatment may cause psychosocial stress.
- Good metabolic control improves psychosocial well-being.
- Identifying people early in the disease course through screening and introducing long-term intensive treatment does not cause psychosocial harm.
- Clinicians and public health systems implementing early detection and intensive treatment protocols for type 2 diabetes do not need to worry that these may have a long-term adverse impact on peoples' psychosocial well-being.

### **Abstract**

**Aims** To present the longer-term impact of multifactorial treatment of type 2 diabetes on self-reported health status, diabetes-specific quality of life, and diabetes treatment satisfaction at 10-year follow up of the ADDITION-Europe trial.

**Methods** The ADDITION-Europe trial enrolled 3057 individuals with screen-detected type 2 diabetes from four centres [Denmark, the UK (Cambridge and Leicester) and the Netherlands], between 2001 and 2006. Participants were randomized at general practice level

to intensive treatment or to routine care . The trial ended in 2009 and a 10-year follow-up was performed at the end of 2014. We measured self-reported health status (36-item Short-Form Health Survey and EQ-5D), diabetes-specific quality of life (Audit of Diabetes-Dependent Quality of Life questionnaire), and diabetes treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire) at different time points during the study period. A mixed-effects model was applied to estimate the effect of intensive treatment (intention-to-treat analyses) on patient-reported outcome measures for each centre. Centre-specific estimates were pooled using a fixed effects meta-analysis.

**Results** There was no difference in patient-reported outcome measures between the routine care and intensive treatment arms in this 10-year follow-up study [EQ-5D:  $-0.01$  (95% CI  $-0.03, 0.01$ ); Physical Composite Score (36-item Short-Form Health Survey):  $-0.27$  (95% CI  $-1.11, 0.57$ ), Audit of Diabetes-Dependent Quality of Life questionnaire:  $-0.01$  (95% CI  $-0.11, 0.10$ ); and Diabetes Treatment Satisfaction Questionnaire:  $-0.20$  (95% CI  $-0.70, 0.29$ )].

**Conclusions** Intensive, multifactorial treatment of individuals with screen-detected type 2 diabetes did not affect self-reported health status, diabetes-specific quality of life, or diabetes treatment satisfaction at 10-year follow-up compared to routine care.

## Introduction

A diagnosis of type 2 diabetes is an impactful life event as this disease is associated with micro- and macrovascular complications and reduced self-reported quality of life [1]. The burden of both disease and treatment may lead to psychosocial stress and low levels of treatment satisfaction [2], while better glycaemic control has been shown to improve psychosocial outcomes [3,4]. Furthermore, intensive treatment of cardiovascular risk factors in people with longstanding type 2 diabetes and microalbuminuria has markedly reduced the incidence and progression of complications [5–7], which may also improve longer-term

psychological outcomes.

The balance between potential harm and benefit of a diabetes diagnosis and lifelong multifactorial treatment is particularly important for individuals with screen-detected type 2 diabetes, who have few or no symptoms of the disease but are still encouraged to initiate medical treatment and lifestyle changes following diagnosis. Patient-reported outcome measures (PROMs) are found to be good indicators of self-reported health and self-perceived treatment satisfaction and good predictors of mortality, and are used in many studies to assess health status [8,9].

The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION-Europe), a pragmatic, cluster-randomized controlled trial in general practice in Denmark, England and the Netherlands, found a 17% non-significant relative risk reduction in cardiovascular morbidity and mortality at 5-year follow-up [3] and a 13% non-significant reduction after 10 years of follow-up [10], comparing routine care to the intensive treatment. The ADDITION-Europe trial found no differences in self-reported health status, diabetes-specific quality of life, and diabetes treatment satisfaction between the intensive treatment and the routine care group after 5 years [11]. This suggests that multifactorial, intensive treatment of the intervention group does not influence PROMs in people with screen-detected type 2 diabetes. Previous findings support this result. The UK Prospective Diabetes Study (UKPDS) reported no impact of intensified treatment on self-reported health in people with a recent clinical diabetes diagnosis, although self-reported health was affected by the complications of the disease [4]. Likewise, the ACCORD trial found no clinically significant difference in PROMs between treatment groups after 4 years of follow-up [12]. No previous studies have examined the association between multifactorial diabetes treatment and PROMs in people with screen-detected type 2 diabetes over a longer-term follow-up. A longer follow-up period provides greater opportunity to detect differences

that may arise only after several years of living with the disease and its treatment.

Furthermore, analyses based on more than two time points enable the quantification of the magnitude of change in either group. We therefore evaluated the effect of multifactorial diabetes treatment on self-reported health status [36-item Short-Form Health Survey (SF-36) and the EQ-5D questionnaire], diabetes-specific quality of life [Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire], and diabetes treatment satisfaction [Diabetes Treatment Satisfaction Questionnaire (DTSQ)] after 10 years of follow-up among people with screen-detected diabetes in the ADDITION-Europe trial.

## **Participants and methods**

The ADDITION-Europe trial consisted of a screening study and a cluster-randomized controlled trial which was performed in four centres in Denmark, the UK (Cambridge and Leicester), and the Netherlands. The design of the ADDITION-Europe trial has been described in detail elsewhere [13–16]. In brief, 343 general practices were randomized to provide intensive multifactorial treatment or routine care to people with newly diagnosed, type 2 diabetes detected by screening. The randomization took place before the start of the screening programme. The diagnosis of type 2 diabetes was based on the WHO 1998 criteria [17]. Individuals were excluded if they had a life expectancy shorter than 12 months, were housebound, pregnant or lactating, or had psychological or psychiatric illness that might invalidate informed consent. A total of 3057 individuals with type 2 diabetes were identified by screening and included in the ADDITION-Europe trial between 2001 and 2006. The intervention ran for 5 years until 31 December 2009 [18]. No attempts were made to maintain differences in treatment between study groups after the end of the intervention. Ten-year follow-up (5-year post-intervention) ended on 31 December 2014 [mean (SD) follow-up 9.6 (3.0) years] [10].

## **Intervention**

General practices in the intensive treatment group were instructed to deliver a multifactorial, intensified target-driven treatment. The multifactorial treatment differed slightly between the centres [15,18]. The treatment targets for the intensive treatment group were: HbA<sub>1c</sub> <53 mmol/mol (7.0%); blood pressure  $\leq$ 135/85 mmHg; cholesterol < 5 mmol/l, if there was no history of coronary heart disease, and <4.5 mmol/l in case of previous cardiovascular disease; and prescription of aspirin if treated with anti-hypertensive medication. The intervention consisted of both pharmacological treatment and promotion of healthy lifestyle. Treatment targets, and the means to achieve the targets, have been described in detail elsewhere [10,18]. The routine care group were advised to follow the national guidelines for type 2 diabetes treatment in the respective countries.

## **Measurements and outcomes**

Clinical and anthropometric measures at baseline and 5 years were collected at clinical examinations in each centre following standard operating procedures. At 10-year follow-up data were retrieved from general practice records and national registers. Information on death prior to 10-year follow-up was collected from national registers and a composite outcome of first cardiovascular event was assessed by an independent adjudication committee in each centre based on the participant's medical records and national registers. Measures are described in detail elsewhere [10].

The PROMs were obtained from self-administrated questionnaires and collected at different time points in each centre. The questionnaires included self-reported health status, diabetes treatment satisfaction and quality of life, and covered both generic and diabetes-specific measures.

The EQ-5D consists of a classification system (EQ-5D Profile) and a visual analogue scale (EQ-VAS) [19,20]. The EQ-5D profile covers five domains of health, namely: mobility; self-

care; usual activities; pain/discomfort; and anxiety/depression. Each domain has three levels of functioning: level 1, no problems; level 2, some problems; and level 3, severe problems.

Responses are summarized and recoded as a number between  $-1$  and  $+1$ , where 0 means death, optimal health is 1 and negative numbers indicate health states rated as worse than death. The EQ-VAS is a graded, vertical line, anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). Participants were requested to mark the point on the EQ-VAS that best indicated their current health state.

The SF-36 generates a profile of scores on eight dimensions of health [21]. The Physical Composite Score (PCS) and Mental Composite Score (MCS) are calculated based on eight dimensions and range likewise from 0 to 100, with the latter indicating the best health state.

ADDQoL examines the impact of diabetes on specific aspects of well-being of study participants, and is designed for clinical and research use [22]. Whereas generic measures of health status (e.g. SF-36) may be strongly affected by non-diabetes-related comorbidity, ADDQoL scores reflect the impact of diabetes-related complications only. The scores range from  $-3$  (a great deal better) to 1 (worse) and are generated by rating of the importance of the item from 3 (very important) to 0 (not at all important). Scores are calculated by multiplying the unweighted responses by the importance rating. The total score is the mean of all the weighted ratings and ranges from  $-9$  (the maximum negative impact of diabetes) to 3 (the maximum positive impact of diabetes).

The DTSQ is used to measure patient satisfaction with diabetes treatment [23]. It consists of a six-item scale assessing treatment satisfaction. The treatment satisfaction score ranges from 0 (very dissatisfied) to 36 (very satisfied).

### **Statistics**

The trial analysis was performed using an intention-to-treat approach, which compared participants according to the randomized treatment allocation, regardless of the intensity of

treatment received. The analyses considered the randomization effect over the entire 10-year follow-up period, even though the active intervention stopped after the 5-year trial period.

The population's PROM characteristics are presented by randomization group, separately for each centre. For continuous variables, means and standard deviations were used, unless the variable had a highly skewed distribution, in which case, medians (25<sup>th</sup> and 75<sup>th</sup> percentiles) are presented. PROMs were collected at different time points at the centres (in Denmark at 0, 5 and 10 years, in Cambridge at 0, 1, 5 and 10 years, and in Leicester and the Netherlands at 0 and 5 years, while no 10-year PROMs data were collected in these latter two centres). For each outcome, the number of missing values is reported.

For PROMs, participants with missing data at the 5-year and the 10-year follow-up are likely to be the individuals who experienced the most serious illness or, alternatively, individuals who do not consider their symptomless diabetes as a serious disease. These missing data can consequently not be assumed to be 'missing completely at random', so simply excluding these participants could have led to selection bias. We therefore performed multiple imputation before analysing data by including clinical variables from baseline and follow-up examinations that could explain the observed pattern of missing data. This approach assumes that data are 'missing at random', i.e. that the missingness pattern is dependent on observed variables. We used the MICE framework [24] to carry out a 60-fold multiple imputation and subsequently summarized results according to Rubin's rules [25]. All further analyses were performed based on these 60 estimates. Individuals who died before the 5-year follow-up or before the 10-year follow-up were excluded from the analyses at those respective time points as they did not contribute to the respective analyses.

Analyses were performed using mixed-effects models with time since baseline as the underlying time scale. This allowed us to accommodate the different measurement time sequences per scale and per centre and make optimal use of all available data. Models had a



fixed time-independent term of 0 at baseline, to reflect the fact that by virtue of the randomized design, baseline values are assumed to be equal in both study arms. The models yield estimates for the time-dependent differences in the respective outcomes by treatment arm. We use the mixed-effect model to estimate the differences for each centre, when comparing the intensive treatment with routine care. Estimates were given as unstandardized  $\beta$ -coefficients and afterwards pooled across the centres using a fixed-effects meta-analysis with inverse variance weighting; that is, with a fixed centre effect and common intervention effect and weighting for the different numbers of observations per centre. This method was used because, in the context of a randomized controlled trial, the estimand can reasonably be assumed to be the same across centres.

The  $I^2$  statistic, representing the proportion of variability between centres due to heterogeneity, was calculated. A sensitivity analysis was performed repeating all analytical steps with a complete-case approach (non-imputed outcome data). For all outcomes, the standard errors were adjusted to account for intra-cluster correlation, with the general practices as clusters. The intervention effect was reported together with a 95% CI. All analyses were performed using STATA 15.

### **Ethics**

The ADDITION-Europe trial was approved by local ethics committees in each centre. All participants provided written informed consent before inclusion in the original trial.

### **Results**

A total of 3057 individuals participated in the ADDITION-Europe trial; 1678 in the intensive group and 1379 in the routine care group. The flow of participants is plotted in Fig. 1.

Baseline demographics and other participant characteristics were similar between the intervention and control groups (Table 1). All the available PROMs included in the multiple imputation analyses are shown in Table 2. The table contains time point, numbers, number of missing values and means with standard deviation by centre and randomization group.

The centre-specific and overall estimated differences between randomized groups for each examined PROM are plotted in Figs 2 and 3. There was no statistically significant difference between the intensive treatment group and the routine care group in PROMs, either by centre or in the overall meta-analysed estimates [EQ-5D: estimated difference  $-0.01$  (95% CI  $-0.03, 0.01$ ); EQ-VAS: estimated difference  $-0.46$  (95% CI  $-1.80, 0.87$ ); PCS: estimated difference  $-0.77$  (95% CI  $-1.11, 0.57$ ); MCS: estimated difference  $-0.11$  (95% CI  $-0.87, 0.65$ ); ADDQoL: estimated difference  $-0.01$  (95% CI  $-0.11, 0.10$ ); and DTSQ: estimated difference  $-0.20$  (95% CI  $-0.70, 0.29$ )]. Our meta-analysis models showed no evidence of heterogeneity ( $P$  values for heterogeneity  $>0.05$ ). Sensitivity analyses showed slightly higher mean values for the non-imputed outcomes compared to the imputed, however, there was no material difference in the estimated between-group differences when comparing imputed and non-imputed outcomes (data not shown).

## Discussion

Overall, we found no difference in self-reported health status, diabetes-specific quality of life, and diabetes treatment satisfaction between the intensive and routine care group in the 10-year follow-up of the multicentre ADDITION-Europe trial. This suggests that receiving intensive, multifactorial diabetes treatment after being diagnosed with type 2 diabetes following screening did not influence health status and diabetes-specific quality of life after 10 years.

The PROM results throughout the ADDITION-Europe trial should be seen in light of the concurrent differences in treatment intensity and in the primary outcome. At the 5-year follow-up, the ADDITION-Europe trial found a lower composite cardiovascular disease event

risk in the intensive arm, albeit not at a statistically significant level, while the treatment burden in this arm was higher [18]. In that same time window, the PROM results were similar between the two treatment arms [11].

At the 10-year follow-up the intensive treatment arm still showed a non-statistically significant lower primary event risk compared to the routine care arm [10], but the differences in treatment burden had largely disappeared and both trial arms had good glycaemic control. In this light, we might have expected the PROMs at 10 years to favour the intensive treatment group more than at 5 years, but this was not the case, suggesting that PROMs are not directly driven by medical treatment burden, but perhaps rather by the overall burden of comorbidities.

A strength of the present study is that we had a long follow-up in a large diabetes treatment trial among individuals with screen-detected type 2 diabetes from three different European countries and in different settings, including both urban and rural. This long follow-up period and large sample size enabled us to confidently exclude the presence of potential harmful effects of even relatively modest magnitude. Furthermore, our repeated measures of patient-reported outcomes allowed us to analyse how intensive multifactorial treatment after screen-detected diabetes diagnosis affects PROMs when comparing the intensive to routine care group. Using mixed-effect models allowed us not to exclude participants with either missing baseline or follow-up values. We used validated generic and diabetes-specific questionnaire scales. Parallel consideration of different PROMs has been found to be important in the overall evaluation of diabetes treatment regimens, as these self-reported scales measure different aspects of the influence of disease and treatment on daily life [26].

The present study also has some limitations. Not all centres collected 10-year follow-up questionnaires, hence it was not possible to calculate change estimates for all four centres. In the 10-year follow-up of the trial we had some missing outcome data, which can only be

considered to be 'missing not at random' as one might reasonably expect that the individuals who did not complete the questionnaires were those who were more seriously ill. Although this process was arguably non-differential, affecting the intensive treatment and routine care arms in equal measure, it was important to attempt to limit its impact on the study results. We performed multiple imputation using state-of-the-art methods, which take all available determinants of missing observations into account, but are based on the assumption of 'missing at random'. Although this procedure cannot fully remove the impact of selection, we judged it preferable to a complete-case analysis, which would have accentuated the bias caused by selection. Sensitivity analyses showed no material difference in the results based on imputed and non-imputed (complete-case) analytical approaches. This suggests that the imputation procedure has improved the power of our study, without introducing further bias. Sensitivity analyses excluding the centres Leicester and the Netherlands found similar results, suggesting that, although data were not available from all centres at all time points, the estimates are likely to be robust.

As ADDITION is a randomized controlled trial with similar inclusion criteria and the same intervention in all the four centres, the study populations, intervention and outcome measures are sufficiently homogenous across units to justify the prespecified meta-analysis. Indeed the primary endpoint of the trial (composite cardiovascular event) exhibited no heterogeneity between centres. The meta-analysis performed in this study showed no evidence of heterogeneity, confirming that our approach of using a fixed-effects meta-analysis is appropriate. Our study population was identified by screening and thereby earlier in the disease trajectory than clinically diagnosed people. While some participants had indications of complications at baseline, the prevalence of complications at diagnosis is clearly lower than in other diabetes trials, which recruited people with an established diagnosis. Participants in our study had a mean baseline HbA<sub>1c</sub> of 53 mmol/mol (7%), whereas other diabetes study

populations had mean levels in the range of 58.5–67.2 mmol/mol (7.5–8.3%) [5,27,28]. While 8% of our participants had cardiovascular disease before diagnosis, other studies report prevalence of cardiovascular disease in the range of 22%–35%. The generic PROM levels after 10 years of follow-up of the ADDITION-EUROPE trial were lower compared to the general population in the same age range, which suggests the ADDITION population has a higher disease or treatment burden than the general population. For example, the mean EQ-5D score in the general Danish population (60–69 years) has been reported to be 0.88 for men and 0.84 for women [29]. In ADDITION-Denmark the respective values were 0.84 (men) and 0.78 (women; intensive treatment). For EQ-VAS, the UK score for the general population (65–74 years) was 77.3 [30] compared to 72.4 (intensive treatment) in ADDITION-Cambridge. However, our results also indicate that ADDITION participants experienced a lower burden of disease compared to other diabetes populations. This indicates that results from the ADDITION-Europe cannot directly be extrapolated to healthcare systems in countries with lower performance.

In the ACCORD trial [12], participants who were on average 2 years older than our participants, with a mean diabetes duration of 9–10 years, had a mean PCS of 37.4 compared to 41.2 in ADDITION-Cambridge. The PANORAMA study [34], a multinational study of people with type 2 diabetes with a mean age of 65.9 years and a mean diabetes duration of 8.9 years, found a relatively negative impact of diabetes on quality of life (ADDQoL –1.69) compared to the ADDITION trial (Denmark: –0.80, Cambridge: –1.05). The study reported a diabetes treatment satisfaction score (DTSQ: 29.8) comparable to the ADDITION trial (Denmark: 30.2, Cambridge: 29.5) [12,26]. Our results with regard to the impact of intensive treatment on self-reported health status, diabetes-specific quality of life, and diabetes treatment satisfaction are in line with findings from other studies. The UKPDS found that intensive treatment of blood glucose did not affect self-reported health status [4]. The ACCORD trial found a small but not

clinically relevant difference in the physical component score of the SF-36 between the intensive glycaemic control and the comparison group in a 4-year follow-up [12]. In this 10-year follow-up of individuals identified with type 2 diabetes by screening, we found that levels of self-reported health status were higher than in clinically detected diabetes populations with longer diabetes duration. We found no association between intensive treatment and self-reported health status or quality of life compared to routine care. These results indicate that intensive, multifactorial treatment of individuals with type 2 diabetes did not adversely affect patient-reported outcome measures.

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### **Competing interests**

None declared.

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FIGURE 1 Flow of practices and participants in follow-up of ADDITION-Europe.

FIGURE 2 Estimated differences in EQ-5D and the its visual analogue scale component (EQ-VAS) between the routine care (RC) and intensive treatment (IT) groups at 10 years of follow-up. Estimated differences are unstandardized  $\beta$  coefficients between RC and IT.

FIGURE 3 Estimated differences in physical composite score (PCS), mental composite score (MCS; both from the SF-36), Audit of Diabetes Quality of Life (ADDQoL) and Diabetes Treatment Satisfaction Questionnaire (DTSQ) between the routine care and intensive treatment groups at 10-year of follow-up of the ADDITION-Europe trial. Estimated differences are unstandardized  $\beta$ -coefficients between routine care (RC) and intensive

treatment (IT). SF-36, 36-item Short Form Health Survey.

Accepted Article

**Table 1** Baseline characteristics of participants in ADDITION-Europe

	Routine care		Intensive treatment	
		<i>N</i> = 1379		<i>N</i> = 1678
Baseline characteristics	Value	Total with data available	Value	Total with data available
Men, <i>n</i> (%)	790 (57.3)	1379	981 (58.5)	1678
Mean (SD) age at diagnosis, years	60.2 (6.8)	1379	60.3 (6.9)	1678
White ethnicity, <i>n</i> (%)	1246 (93.4)	1334	1539 (95.8)	1607
Employed, <i>n</i> (%)	425 (42.0)	1013	482 (40.3)	1197
History of myocardial infarction, <i>n</i> (%)	79 (6.1)	1286	109 (6.8)	1593
History of stroke, <i>n</i> (%)	24 (1.9)	1270	45 (2.9)	1558
Current smokers, <i>n</i> (%)	375 (27.8)	1347	444 (26.9)	1649
Median (IQR) units of alcohol /week	4.0 (1 to 13)	1183	4.0 (1 to 13)	1492

Mean (SD) BMI, kg/m <sup>2</sup>	31.6 (5.6)	1342	31.6 (5.6)	1615
Mean (SD) weight, kg	90.3 (17.6)	1344	90.9 (17.5)	1615
Mean (SD) HbA <sub>1c</sub> , mmol/mol	53.5 (16.7)	1298	53.3 (17.3)	1591
Mean (SD) systolic blood pressure, mmHg	149.8 (21.3)	1346	148.5 (22.1)	1617
Mean (SD) diastolic blood pressure, mmHg	86.5 (11.3)	1346	86.1 (11.1)	1618
Mean (SD) total cholesterol, mmol/l	5.6 (1.2)	1300	5.5 (1.1)	1593

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IQR, interquartile range.

**Table 2** Earliest available patient-reported outcome measures, number of observations and time point, ADDITION-Europe

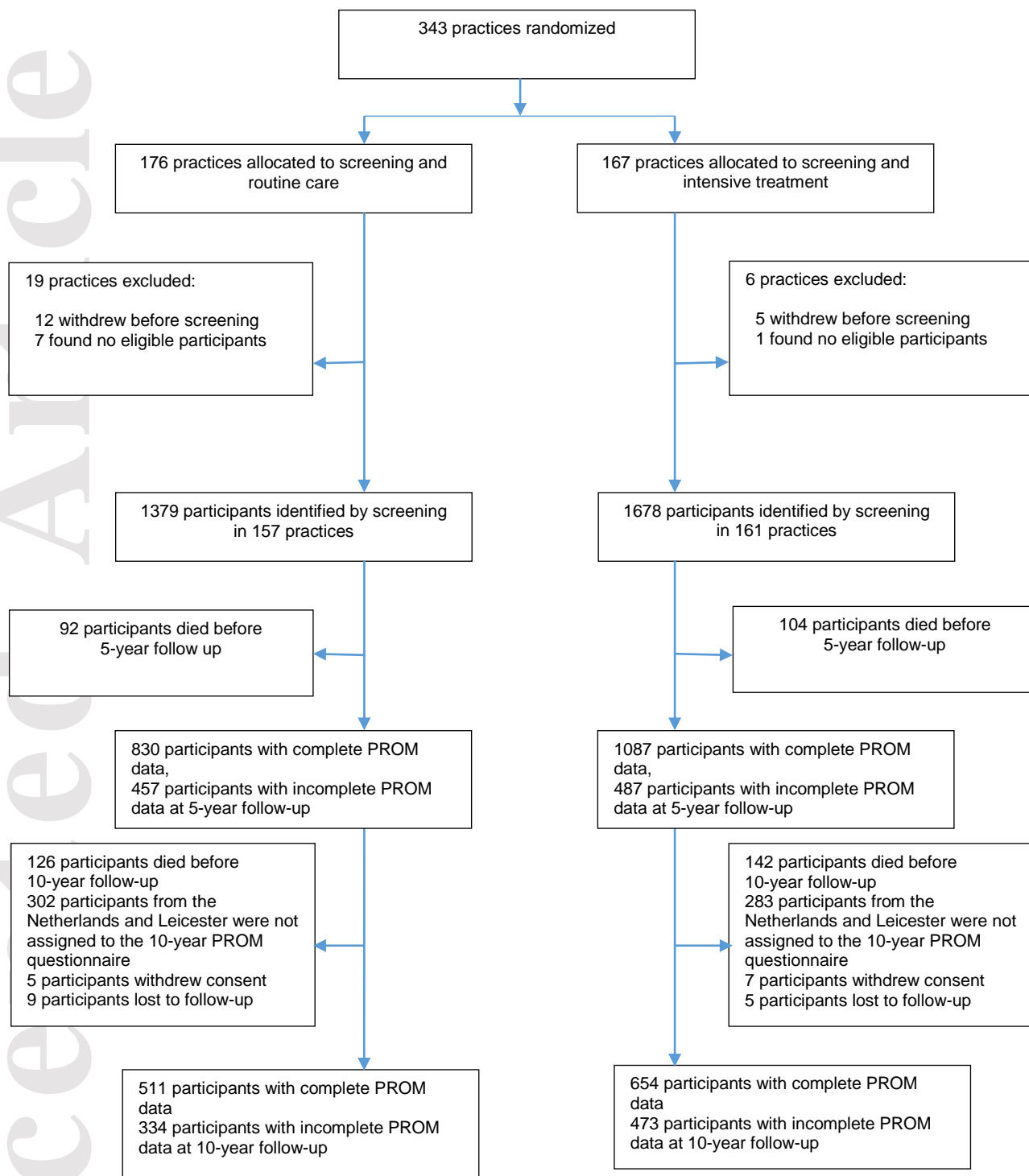
PROMs	Denmark <i>N</i> = 1533				Cambridge <i>N</i> = 867				Leicester <i>N</i> = 159				The Netherlands <i>N</i> = 498				
	IT		RC		IT		RC		IT		RC		IT		RC		
T	n/	Mean (SD)	n/	Mean (SD)	n/	Mean (SD)	n/	Mean (SD)	n/	Mean (SD)	n/	Mean (SD)	n/	Mean (SD)	n/	Mean (SD)	
	missing		missing			missing			missin		missing		missing		missing		
									g								
EQ-5D	0	861/49	0.84 (0.2)	597/26	0.85 (0.2)	443/9	0.82 (0.2)	409/6	0.81 (0.2)	53/8	0.73 (0.3)	68/30	0.82 (0.2)	233/22	0.81 (0.2)	215/28	0.82 (0.2)
	5	696/142	0.85 (0.2)	463/115	0.84 (0.2)	351/77	0.81 (0.2)	312/67	0.83 (0.2)	60/1	0.75 (0.3)	85/10	0.79 (0.2)	176/70	0.86 (0.2)	144/85	0.82 (0.3)
	10	520/194	0.86 (0.2)	358/156	0.85 (0.2)	202/184	0.79 (0.2)	174/174	0.77 (0.3)		-		-		-		-
EQ-VAS	0	824/86	76.0 (16.4)	574/49	76.1 (16.2)		-		-		-		-	184/71	75.1 (17.3)	180/63	76.4 (16.2)
	5	692/176	76.8 (16.9)	462/116	76.4 (18.5)	355/73	76.1 (18.0)	316/63	78.4 (16.4)	60/1	78.3 (16.3)	88/7	74.8 (18.4)	175/71	76.5 (13.7)	144/85	75.3 (15.6)
	10	517/197	77.1 (17.4)	370/116	76.6 (16.8)	201/184	75.8 (17.0)	169/175	75.0 (17.4)		-		-		-		-

PCS	0	845/65	47.0 (9.8)	593/30	47.1 (9.5)	358/94	45.5 (11.3)	351/64	45.0 (10.9)	-	-	-	-				
	5	666/172	46.7 (10.0)	428/150	46.7 (9.6)	350/78	43.9 (11.6)	310/69	44.5 (11.3)	59/2	44.3 (11.4)	84/11	43.3 (10.5)	177/69	46.8 (10.4)	144/85	47.0 (10.5)
	10	465/249	46.4	336/148	45.9 (10.0)	189/196	41.6 (11.9)	175/169	40.8 (11.5)	-	-	-	-				
MCS	0	845/65	54.1 (9.1)	593/30	54.0 (9.3)	358/94	52.8 (9.8)*	351/64	52.7 (9.2)*	-	-	-	-				
	5	666/172	55.3 (9.1)	428/150	54.9 (8.5)	350/78	53.4 (10.6)	310/69	54.6 (8.4)	59/2	50.9 (10.1)	84/11	52.2 (9.9)	177/69	54.3 (8.2)	144/85	53.7 (7.4)
	10	465/249	54.3 (9.2)	336/148	53.6 (9.2)	189/196	53.7 (9.3)	175/169	53.7 (9.3)	-	-	-	-				
ADDQoL	5	553/285	-0.73 (1.2)	348/230	-0.69 (1.1)	315/113	-0.84 (1.3)	271/108	-0.87 (1.3)	50/11	-1.20 (1.8)	76/19	-2.39 (2.5)	169/77	-0.55 (0.9)	135/94	-0.55 (0.9)
	10	503/211	-0.70 (1.0)	356/158	-0.74 (1.2)	201/184	-0.93 (1.3)	176/168	-0.92 (1.1)	-	-	-	-				
DTSQ	5	649/189	30.9 (6.2)	405/173	30.1 (6.7)	344/84	31.5 (4.9)	305/74	31.2 (5.4)	60/1	33.0 (3.8)	85/10	29.1 (7.3)	174/72	31.2 (5.6)	140/89	31.0 (5.6)
	10	499/215	31.4 (5.8)	345/169	31.1 (6.3)	201/184	31.1 (5.5)	178/166	31.3 (5.1)	-	-	-	-				

ADDQoL, Audit of Diabetes-Dependent Quality of Life; DTSQ, Diabetes Treatment Satisfaction Questionnaire; EQ-5D, Euroqol 5 Dimensions; EQ-VAS, visual analogue scale of EQ-5D; IT, intensive treatment; PCS, Physical Composite Score (SF-36); MCS, Mental Composite Score (SF-36); RC, routine care; SF-36, 36-item Short-Form Health Survey.

T = time since inclusion: 0, 1 or 5 years of follow-up. \*PCS and MCS from Cambridge were measured at 1 year.





**Figure 1.** Flow of practices and participants in follow-up of ADDITION-Europe

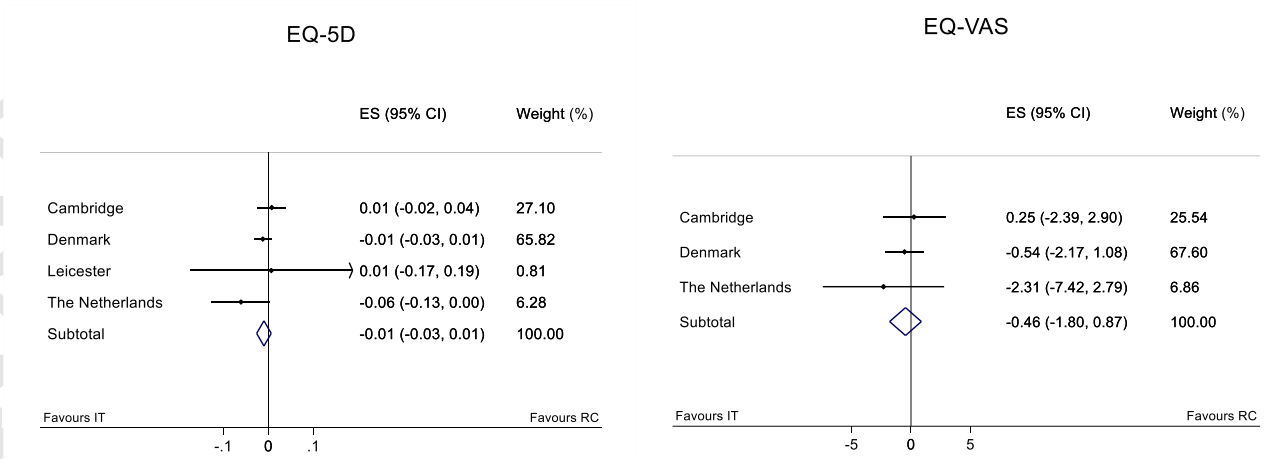


Figure 2. Estimated differences in EQ-5D and EQ-VAS between the RC and IT groups at 10 years of follow-up, ADDITION-Europe

EQ-5D: Euroqol 5 Dimensions – EQ-VAS: Visual Analogue Scale

IT: Intensive treatment - RC: Routine care

Estimated differences is unstandardised beta-coefficients between RC and IT

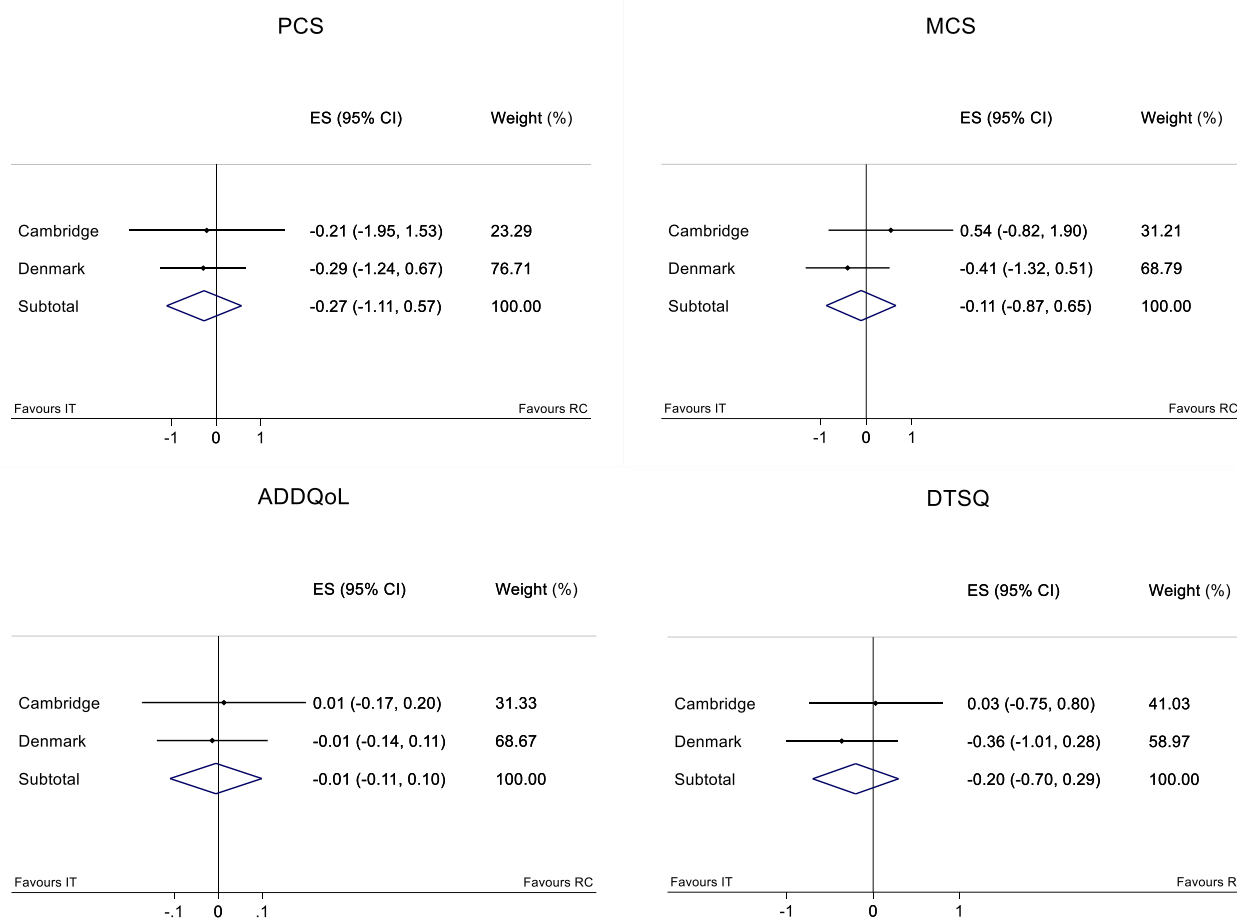


Figure 3. Estimated differences in PCS, MCS, ADDQoL and DTSQ between the RC and IT groups at ten-year of follow-up, ADDITION-Europe

SF36: 36-item Short Form Health Survey – PCS: physical composite scale from SF36 – MCS: mental composite scale from SF36 ADDQoL: Audit of Diabetes Quality of Life, DTSQ: Diabetes Treatment Satisfaction Questionnaire

IT: Intensive treatment, RC: Routine care

Estimated differences is unstandardised beta-coefficients between RC and IT