ELECTRONIC SUPPLEMENTARY MATERIAL

Adults with early-onset type 2 diabetes (aged 18-39 years) are severely underrepresented in diabetes clinical research trials

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Abbreviations

CVD – cardiovascular disease

DPP4i – dipeptidyl peptidase 4 inhibitor

DSMES – diabetes self-Management education and support

GLP-1RA – glucagon-like peptide-1 receptor agonist

GLT – glucose-lowering therapy

IQR – interquartile range

NR – not reported

SGLT2i – sodium-glucose co-transporter 2 inhibitor

TZD - thiazolidinedione
Electronic Supplementary Methods

Study Selection

Firstly, we searched for published manuscripts (from inception to 27th September 2019) reporting demographic data of the study populations recruited to cardio-renal outcomes trials in adults with type 2 diabetes. This included both ongoing (but fully recruited) and completed trials. To do this, we:

i. Searched the online database, PubMed, using search terms related to type 2 diabetes, mortality and cardio-renal outcomes.

ii. Examined the reference lists of review articles and meta-analyses identified by our search.

iii. Examined the reference list of the ADA-EASD consensus report for the management of hyperglycaemia in adults with type 2 diabetes [1].

Secondly, we identified studies contained within the Phase III research programmes for empagliflozin and liraglutide through a targeted search for trials in the “EMPA-REG” and “LEAD” programmes, respectively, and for manufacturer-funded trials examining the efficacy of sitagliptin on improving glycaemic control in isolation or alongside alternative glucose-lowering therapies (GLTs). We pre-specified trials of empagliflozin, liraglutide and sitagliptin as they:

a) Are representative of their class of therapy.

b) Are the most commonly prescribed, were the first licensed worldwide or had the earliest cardio-renal outcomes data.

c) Have Phase III research programmes that are representative of those required for modern licencing of pharmacological GLTs in type 2 diabetes.
Thirdly, prominent trials of diabetes self-management education and support (DSMES) and intensive lifestyle interventions (diet and/or structured exercise training) were identified by review of the ADA-EASD consensus report for management of hyperglycaemia in adults with type 2 diabetes [1], and subsequent examination of relevant reference lists. Specifically, we selected six DSMES trials that were highlighted within a recent narrative review as those examining the most well-established DSMES programmes in type 2 diabetes over the past 10 years [2], and supplemented these with trials recruiting more than 500 participants identified in two systematic reviews of DSMES on glycaemic control and all-cause mortality, respectively [3, 4]. One trial was excluded because it recruited participants with type 1 or type 2 diabetes [5], whilst another was excluded because it examined both DSMES and, in a subset, concurrent pharmacological therapy [6].

We selected three dietary intervention trials which were cited directly within the ADA-EASD consensus report [1], examining the impact of meal replacement therapy, a Mediterranean-style diet and the “Dietary Approaches to Stop Hypertension” (DASH) diet. We included these trials as they were specifically in type 2 diabetes and did not include cited trials that recruited participants with overweight or obesity with or without type 2 diabetes. We also selected representative trials of low-fat, low-carbohydrate, low-glycaemic index, and high-protein diets from two systematic reviews cited within the ADA-EASD consensus report [7, 8]. A large RCT of the commercially-available Weight Watchers programme was identified [9], but it did not report the age of recruited population and was thus excluded.

To explore studies of supervised exercise training, we selected a large RCT which was cited directly in the ADA-EASD consensus report [1], supplemented by a further five trials which examined the impact of exercise training in more than 100 adults with type 2 diabetes via five systematic reviews that were also cited [10–14]. The large “Early Actid” trial (more than 500
participants) was selected from a systematic review of pedometer use to support light-intensity (walking) physical activity in type 2 diabetes [15]. However, this trial examined the effect of dietary counselling with or without pedometer use and was subsequently categorised as a DSMES trial within our analyses.

Data Extraction and Analysis

We extracted data from selected manuscripts on the number of participants recruited \((n)\), the age eligibility criteria, and the age of the recruited population. The latter were extracted as mean and standard deviation \((SD)\) or median and interquartile range \((IQR)\), as reported. SD was calculated from standard error of the mean \((SE)\) or 95 % confidence intervals where required [16]. The pooled mean age of individuals recruited to various groups of studies (e.g. all studies collectively, cardio-renal outcomes trials alone, Phase III trials alone) were summarised as a weighted mean accounting for differences in study sample size.
**Electronic Supplementary Results**

*ESM Table 1 – Details of all studies reviewed*

| First Author (year) [study ref.] | Trial Acronym | Study Category                  | Intervention and Comparator                                                                 | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) |
|----------------------------------|--------------|---------------------------------|---------------------------------------------------------------------------------------------|-------------------|-------------------------------|-------------------------------------|
| **Completed cardiovascular and/or renal outcomes trials** |              |                                 |                                                                                             |                   |                               |                                     |
| Turner (1998) [17]               | UKPDS 34     | Intensive glucose lowering      | Intensive therapy with metformin vs conventional treatment; target fasting plasma glucose concentration of 6mmol/L | 1704             | 25                            | 53 (8)                             | 4.0                               |
| Turner (1998) [18]               | UKPDS 33     | Intensive glucose lowering      | Intensive therapy with a sulphonylurea or insulin vs conventional treatment; target fasting plasma glucose concentration of 6mmol/L | 3867             | 25                            | 53.3 (8.6)                         | 4.8                               |
| Duckworth (2009) [19]            | VADT         | Intensive glucose lowering      | Intensive vs standard therapy with multiple agents according to pre-specified algorithm (stratified by BMI); target 1.5% absolute reduction in HbA1c in intensive vs standard therapy group | 1791             | 41                            | 60.4 (9.0)                         | Not eligible                      |
| Gerstein (2008) [20]             | ACCORD       | Intensive glucose lowering      | Intensive (individualised) therapy with multiple agents vs standard therapy; target HbA1c ≤ 6.0% (7.0 – 7.9% in standard therapy group) | 10251            | 40                            | 62.2 (6.8)                         | Not eligible                      |
| Patel (2008) [21]                | ADVANCE      | Intensive glucose lowering      | Intensive therapy with gliclazide and other therapies where required vs standard therapy; target HbA1c ≤ 6.5% (target in standard therapy group as per local guidelines) | 11140            | 55                            | 66 (6)                             | Not eligible                      |
| Kooy (2009) [22]                 | HOME         | Specific GLT – Metformin        | Metformin vs placebo                                                                        | 390              | 30                            | 61.3 (10.3)                        | 1.5                               |
| Neal (2017) [23]                 | CANVAS / CANVAS-R | Specific GLT – SGLT2i               | Canagliflozin vs placebo                                                                    | 10142            | 30                            | 63.3 (8.3)                         | 0.2                               |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) | Proportion Aged 18 to 39 years (%) |
|---------------------------------|--------------|----------------|-------------------------------|------------------|-------------------------------|-------------------------------------|-----------------------------------|
| Perkovic (2019) [24]            | CREDENCE     | Specific GLT – SGLT2i | Canagliflozin vs placebo      | 4401             | 30                            | 63.0 (9.2)                          | 0.5                               |
| Wiviott (2019) [25]             | DECLARE-TIMI 58 | Specific GLT – SGLT2i | Dapagliflozin vs placebo       | 17160            | 40                            | 64.0 (6.8)                          | Not eligible                      |
| Zinman (2015) [26]              | EMPA-REG OUTCOME | Specific GLT – SGLT2i | Empagliflozin vs placebo       | 7020             | 18                            | 63.0 (8.7)                          | 0.3                               |
| Gerstein (2019) [27]            | REWIND       | Specific GLT – GLP-1RA | Dulaglutide vs placebo         | 9901             | 50                            | 66.2 (6.5)                          | Not eligible                      |
| Hernandez (2018) [28]           | HARMONY      | Specific GLT – GLP-1RA | Albigrutide vs placebo         | 9463             | 40                            | 64.1 (8.7)                          | Not eligible                      |
| Husain (2019) [29]              | PIONEER 6    | Specific GLT – GLP-1RA | Semaglutide (oral) vs placebo  | 3183             | 50                            | 66 (7)                              | Not eligible                      |
| Marso (2016a) [30]              | SUSTAIN 6    | Specific GLT – GLP-1RA | Semaglutide (subcutaneous) vs placebo | 2397         | 50                            | 64.6 (7.4)                          | Not eligible                      |
| Marso (2016b) [31]              | LEADER       | Specific GLT – GLP-1RA | Liraglutide vs placebo         | 9340             | 50                            | 64.3 (7.2)                          | Not eligible                      |
| Holman (2017) [32]              | EXSCEL       | Specific GLT – GLP-1RA | Exenatide (extended release) vs placebo | 14752       | 18                            | 62 (56 – 68)                        | Not estimated                     |
| Pfeffer (2015) [33]             | ELIXA        | Specific GLT – GLP-1RA | Lixisenatide vs placebo        | 6068             | 30                            | 60.3 (9.7)                          | 1.4                               |
| Gantz (2017) [34]               | OMNEON       | Specific GLT – DPP4i  | Omariglptin vs placebo         | 4192             | 40                            | 63.6 (8.5)                          | Not eligible                      |
| Green (2015) [35]               | TECOS        | Specific GLT – DPP4i  | Sitaglptin vs placebo          | 14671            | 50                            | 65.5 (8.0)                          | Not eligible                      |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|---------------------------------|---------------|----------------|----------------------------|------------------|-----------------------------|--------------------------------------------------------------------------|-------------------------------|
| Rosenstock (2019a) [36]         | CARMELINA     | Specific GLT – DPP4i | Linagliptin vs placebo     | 6979             | 18                          | 65.9 (9.1)                                                              | 0.2                           |
| Rosenstock (2019b) [37]         | CAROLINA      | Specific GLT – DPP4i | Linagliptin vs glimepiride | 6033             | 40                          | 64.0 (9.5)                                                              | Not eligible                   |
| Scirica (2013) [38]             | SAVOR-TIMI53  | Specific GLT – DPP4i | Saxagliptin vs placebo     | 16492            | 40                          | 65.1 (8.6)                                                              | Not eligible                   |
| White (2013) [39]               | EXAMINE       | Specific GLT – DPP4i | Alogliptin vs placebo      | 5380             | 18                          | 61 (IQR NR)b                                                           | Not estimated (normal distribution not assumed) |
| Dormandy (2005) [40]            | PROactive     | Specific GLT – TZD  | Pioglitazone vs placebo    | 5238             | 35                          | 61.8 (7.7)                                                              | 0.2                           |
| Yoshii (2017) [41]              | PROFIT-J      | Specific GLT – TZD  | Pioglitazone vs placebo    | 481              | 55                          | 69.0 (7.2)                                                              | Not eligible                   |
| Vaccaro (2017) [42]             | TOSCA.IT      | Specific GLT – TZD  | Pioglitazone vs sulphonylurea | 3028           | 50                          | 62.3 (6.5)                                                              | Not eligible                   |
| Home (2009) [43]                | RECORD        | Specific GLT – TZD  | Rosiglitazone vs metformin and sulphonylurea dual-therapy | 4447            | 40                          | 58.4 (8.3)                                                              | Not eligible                   |
| Gerstein (2012) [44]            | ORIGIN        | Specific GLT – Insulin | Insulin glargine vs standard care | 12537          | 50                          | 63.5 (7.9)                                                              | Not eligible                   |
| Marso (2017) [45]               | DEVOTE        | Specific GLT – Insulin | Insulin degludec vs insulin glargine | 7637           | 50                          | 65.0 (7.4)                                                              | Not eligible                   |
| Raz (2009) [46]                 | HEART2D       | Specific GLT – Insulin | Postprandial insulin lispro three-times daily vs Neutral Protamine Hagedorn insulin twice daily or insulin glargine once daily | 1115           | 30                          | 61.0 (9.8)                                                              | 1.2                           |
| Lincoff (2014) [47]             | AleCardio     | Other pharmacological therapy | Aleglitazar vs placebo     | 7226             | 18                          | 61 (10)                                                                 | 1.4                           |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|-------------------------------|---------------|----------------|-----------------------------|------------------|-----------------------------|------------------------------------------------------------------|--------------------------------|
| Wing (2013) [48]            | Look AHEAD    | Intensive lifestyle intervention | Intensive lifestyle intervention (promoting weight loss through reduced caloric intake and increased physical activity) vs diabetes support and education | 5145             | 45                          | 58.7 (6.9)                                                      | Not eligible                    |
| Frye (2009) [49]            | BARI 2D       | Surgery and pharmacological therapy approach | Prompt revascularisation with intensive medical therapy vs medical therapy alone and insulin sensitisation vs insulin provision | 2368             | 25                          | 62.4 (8.9)                                                      | 0.4                            |
| Gaede (2003) [50]           | STENO-2       | Multifactorial intervention | Intensive multifactorial intervention (containing stepwise implementation of behaviour modification and pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria, plus aspirin for secondary prevention of CVD) vs standard therapy | 160              | 40                          | 55.1 (7.2)                                                      | Not eligible                    |
| Hansen (2013) [51]          | DCGP          | Multifactorial intervention | Intensive multifactorial intervention containing structured personalised care vs standard therapy | 1381             | 40                          | 65.4 (55.7 – 73.6)b                                            | Not estimated (normal distribution not assumed) |
| Ueki (2017) [52]            | J-DOIT3       | Multifactorial intervention | Intensive multifactorial intervention (targeting hyperglycaemia, dyslipidaemia and hypertension) vs conventional therapy | 2540             | 45                          | 59.0 (6.4)                                                      | Not eligible                    |

**Ongoing cardiovascular and/or renal outcomes trials**

| Cannon (2018) [53] | VERTIS-CV | Specific GLT – SGLT2i | Ertugliflozin vs placebo | 8238 | 40 | 64.4 (8.1) | Not eligible |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|---------------------------------|---------------|----------------|----------------------------|------------------|-------------------------------|------------------------------------------------------------------|-----------------------------|
| Roden (2013) [54]               | EMPA-REG MONO | Specific GLT – SGLT2i | Empagliflozin vs placebo vs sitagliptin (all monotherapy) | 899              | 18                            | 55 (11)                                                          | 7.3                         |
| Häring (2014) [55]              | EMPA-REG MET | Specific GLT – SGLT2i | Empagliflozin vs placebo (all background metformin) | 638              | 18                            | 55.7 (9.9)                                                      | 4.6                         |
| Häring (2013) [56]              | EMPA-REG METSU | Specific GLT – SGLT2i | Empagliflozin vs placebo (all background metformin and sulphonylurea) | 666              | 18                            | 57.1 (9.2)                                                      | 2.5                         |
| Kovacs (2014) [57]              | EMPA-REG PIO | Specific GLT – SGLT2i | Empagliflozin vs placebo (all background pioglitazone with or without metformin) | 498              | 18                            | 54.5 (9.8)                                                      | 5.7                         |
| Rosenstock (2015) [58]          | EMPA-REG BASAL | Specific GLT – SGLT2i | Empagliflozin vs placebo (all background basal insulin with or without metformin and/or sulphonylurea) | 494              | 18                            | 58.8 (9.9)                                                      | 2.3                         |
| Rosenstock (2014) [59]          | EMPA-REG MDI | Specific GLT – SGLT2i | Empagliflozin vs placebo (all background multiple daily injections of insulin with or without metformin) | 563              | 18                            | 56.7 (9.5)                                                      | 3.1                         |
| Ridderstråle (2014) [60]        | EMPA-REG H2H SU | Specific GLT – SGLT2i | Empagliflozin vs glimepiride (all background metformin) | 1545             | 18                            | 56.0 (10.4)                                                     | 5.1                         |
| Tikkanen (2015) [61]            | EMPA-REG BP | Specific GLT – SGLT2i | Empagliflozin vs placebo (various, but stable, background GLTs but all undergoing pharmacological treatment for hypertension) | 823              | 18                            | 62 (9)                                                          | 0.5                         |
| Barnett (2014) [62]             | EMPA-REG RENAL | Specific GLT – SGLT2i | Empagliflozin vs placebo (various, but stable, background GLTs, excluding SGLT2is, but all with eGFR ≥ 15 and < 90 ml/min per 1.73m²) | 290              | 18                            | 62.6 (8.3)                                                     | 0.2                         |

*Representative Phase III studies of glucose-lowering therapies used routinely in clinical practice*
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|---------------------------------|--------------|----------------|----------------------------|------------------|-----------------------------|--------------------------------------------------------------------------------|----------------------------------|
| Marre (2009) [63]               | LEAD 1       | Specific GLT – GLP-1RA | Liraglutide (in combination with glimepiride with or without rosiglitazone) vs placebo (plus glimepiride with or without rosiglitazone) | 1041             | 18                         | 56 (10)                                                                        | 4.5                              |
| Nauck (2009) [64]               | LEAD 2       | Specific GLT – GLP-1RA | Liraglutide vs placebo vs glimepiride (all in combination with metformin) | 1091             | 18                         | 57 (9)                                                                         | 2.3                              |
| Garber (2009) [65]              | LEAD 3       | Specific GLT – GLP-1RA | Liraglutide vs glimepiride (all on various background monotherapy; excluding insulin) | 746              | 18                         | 53.0 (10.8)                                                                    | 9.7                              |
| Zinman (2009) [66]              | LEAD 4       | Specific GLT – GLP-1RA | Liraglutide vs placebo (all in combination with metformin and rosiglitazone) | 533              | 18                         | 55 (10)                                                                        | 5.5                              |
| Buse (2009) [67]                | LEAD 5       | Specific GLT – GLP-1RA | Liraglutide vs exenatide (all on background maximal tolerated doses of metformin, sulphonylurea or both) | 464              | 18                         | 56.7 (10.3)                                                                    | 4.3                              |
| Russell-Jones (2009) [68]       | LEAD 6       | Specific GLT – GLP-1RA | Liraglutide vs placebo vs insulin glargine (all in combination with metformin and glimepiride and all on various background mono-or combination therapies; excluding insulin) | 581              | 18                         | 57.5 (9.9)                                                                     | 3.1                              |
| Pratley (2010) [69]             | 1860-LIRA-DPP4 | Specific GLT – GLP-1RA | Liraglutide vs sitagliptin (on background metformin only) | 665              | 18                         | 55.3 (9.2)                                                                     | 3.8                              |
| Aschner (2006) [70]             | Sitagliptin Study 021 | Specific GLT – DPP4i | Sitagliptin vs placebo (various background therapies; oral GLTs only) | 741              | 18                         | 54.2 (9.9)                                                                     | 6.2                              |
| Mohan (2009) [71]               | -            | Specific GLT – DPP4i | Sitagliptin vs placebo (various background therapies; excluding insulin) | 530              | 18                         | 50.9 (9.3)                                                                     | 10.0                             |
| Charbonnel (2006) [72]          | Sitagliptin Study 020 | Specific GLT – DPP4i | Sitagliptin vs placebo (both on background of metformin only) | 701              | 18                         | 54.5 (10.2)                                                                    | 6.4                              |
| Hermansen (2007) [73]           | Sitagliptin Study 035 | Specific GLT – DPP4i | Sitagliptin vs placebo (both groups had further groups of background glimepiride only or glimepiride and metformin) | 441              | 18                         | 56.0 (9.5)                                                                     | 3.7                              |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|---------------------------------|--------------|----------------|-------------------------------|------------------|--------------------------------|---------------------------------------------------------------------|----------------------------------|
| Rosenstock (2006) [74]          | Sitagliptin Study 019 | Specific GLT – DPP4i | Sitagliptin vs placebo (both on background of pioglitazone only) | 353              | 18                             | 56.3 (10.8)                                                         | 5.4                              |
| Vilsbøll (2010) [75]            | Sitagliptin Study 051 | Specific GLT – DPP4i | Sitagliptin vs placebo (both on background of long- or intermediate-acting or premixed insulin with or without metformin only) | 641              | 21                             | 57.8 (9.2)                                                         | 2.1                              |
| Dobs (2013) [76]                | -             | Specific GLT – DPP4i | Sitagliptin vs placebo (both on background on metformin and rosiglitazone only) | 262              | 18                             | 54.5 (9.0)                                                         | 4.3                              |
| Goldstein (2007) [77]           | Sitagliptin Study 036 | Specific GLT – DPP4i | Sitagliptin and metformin dual-therapy vs sitagliptin monotherapy vs metformin monotherapy vs placebo (various background therapies; oral GLTs only) | 1091             | 18                             | 53.5 (9.9)                                                         | 7.1                              |
| Yoon (2011) [78]                | Sitagliptin Protocol 064 | Specific GLT – DPP4i | Sitagliptin and pioglitazone dual-therapy vs pioglitazone monotherapy (on background of diet and exercise counselling only) | 520              | 18                             | 51.0 (10.7)                                                         | 13.0                             |
| Aschner (2010) [79]             | Sitagliptin Study 049 | Specific GLT – DPP4i | Sitagliptin vs metformin (on background of diet and exercise counselling only) | 894              | 18                             | 56.0 (10.5)                                                         | 5.3                              |
| Nauck (2007) [80]               | Sitagliptin Study 024 | Specific GLT – DPP4i | Sitagliptin vs glipizide (both on background of metformin only) | 1172             | 18                             | 56.7 (9.6)                                                         | 3.3                              |
| Chan (2008) [81]                | -             | Specific GLT – DPP4i | Sitagliptin vs placebo followed by glipizide (on background of diet and exercise counselling only or insulin monotherapy, and all with 24hr creatinine clearance ≥30 and <50 ml/min and not on dialysis) | 91               | 18                             | 67.9 (9.8)                                                         | 0.2                              |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator                                                                                                                                                                                                 | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|----------------------------------|---------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------|--------------------------------------------------------------------------|----------------------------------|
| Sone (2002) [82]                 | JDCS          | DSMES          | Lifestyle modification programme focussing on dietary habits, physical activity and medications adherence, delivered during standard outpatient clinics and via frequent telephone counselling vs ongoing standard care | 2205              | 40                            | 59.4 (7.4)                                                              | Not eligible                     |
| Young (2005) [83]                | PACCTS        | DSMES          | Call centre support intervention with frequency of calls based on previous HbA1c measurement vs ongoing standard care                                                                                                             | 591               | NR                            | 67.0 (NR)                                                               | Not estimated (SD not reported)  |
| Deakin (2006) [84]               | X-PERT        | DSMES          | Face-to-face group-based education aiming to develop skills and build confidence to support informed self-management decisions vs ongoing standard care plus prearranged individual appointments with dietician, practice nurse and General Practitioner. | 314               | 18                            | 61.6 (10.4)                                                            | 1.5                              |
| Adolfsson (2007) [85]            | “Uppsala study” | DSMES      | Group education focussing on empowerment and dealing with different themes of self-care in type 2 diabetes vs standard ongoing care                                                                                     | 88                | NR                            | 63.1 (9.4)                                                             | 0.5                              |
| Ko (2007) [86]                   | SIDEP         | DSMES          | Inpatient 5-day education programme with curriculum based on knowledge of type 2 diabetes, teaching of self-glucose monitoring, injection techniques, sick-day care, meal planning, physical activity, foot inspection and management of hypoglycaemia vs brief “conventional” education | 437               | NR                            | 53.7 (8.3)                                                             | 3.8                              |

Prominent studies examining the effects of diabetes self-management education and support, and intensive lifestyle interventions in adult type 2 diabetes
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|---------------------------------|---------------|----------------|-------------------------------|------------------|-----------------------------|----------------------------------------------------------------------------|----------------------------------|
| Davies (2008) [87] | DESMOND | DSMES | Structured group education programme delivered in the community focussing on empowerment and encouragement of participants to consider their own personal lifestyle risk factors and medication self-management vs standard ongoing care | 824 | 18 | 59.5 (12.2) | 4.6 |
| Sturt (2008) [88] | Diabetes Manual | DSMES | Diabetes Manual workbook with face-to-face introduction and telephone support vs standard ongoing care | 245 | 18 | 62.0 (NR) | Not estimated (SD not reported) |
| Gary (2009) [89] | Project Sugar 2 | DSMES | Intensive multifactorial intervention using evidence-based clinical algorithms and culturally-tailored intervention action plans to address traditional and non-traditional cardiovascular risk factors vs telephone-based ‘minimal’ education | 488 | 25 | 58.0 (11.0) | 4.2 |
| Trento (2010) [90] | ROMEO | DSMES | Group-based education focussing on modifiable lifestyle risk factors and medication self-management through hands-on activities, group work, problem-solving, real-life simulations and role playing vs ongoing standard care | 815 | 18 | 69.3 (8.1) | 0.01 |
| Walker (2011) [91] | I DO | DSMES | Regular telephone calls with health educator focussing on medications adherence and, secondarily, healthy eating and physical activity vs printed education materials | 526 | 30 | 55.5 (7.3) | 1.2 |
| Ali (2016) [92] | CARRS | DSMES | Multicomponent care model including face-to-face and telephone sessions with non-physician care coordinator focussing on modifiable lifestyle risk factors, medication management, glucose self-monitoring and stress management vs ongoing standard care | 1146 | 35 | 54.2 (9.2) | 4.9 |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|----------------------------------|---------------|----------------|----------------------------|-------------------|-------------------------------|--------------------------------------------------------------------------|-------------------------------|
| Odnoletkova (2016) [93]          | COACH         | DSMES          | Multifactorial tele-coaching intervention focussing on empowerment and encouragement of individuals to identify and self-manage their individuals risk factor targets vs ongoing standard care | 574               | 18                            | 63.1 (8.8)                                                              | 3.1                           |
| Andrews (2011) [94]              | Early ACTID    | DSMES (diet ± physical activity only) | Intensive dietary counselling vs intensive dietary counselling plus pedometer-based activity programme vs standard ongoing care | 593               | 30                            | 60.0 (10.3)                                                             | 2.1                           |
| Lean (2017) [95]                 | DiRECT        | Intensive Lifestyle Intervention (Diet) | Total dietary replacement and structured support for long-term weight loss maintenance (plus withdrawal of glucose-lowering medications) vs current best-practice guidelines | 298               | 20                            | 54.4 (7.5)                                                             | 2.0                           |
| Jenkins (2008) [96]              | -             | Intensive Lifestyle Intervention (Diet) | Low-glycaemic index diet vs high-cereal fibre diet | 210               | 21                            | 60.5 (9.4)                                                             | 1.1                           |
| Davis (2009) [97]                | -             | Intensive Lifestyle Intervention (Diet) | Low-carbohydrate diet vs low-fat diet | 105               | 18                            | 53.5 (6.2)                                                             | 1.0                           |
| Esposito (2009) [98]             | -             | Intensive Lifestyle Intervention (Diet) | Low-carbohydrate Mediterranean-style diet vs low-fat diet | 215               | 30                            | 52.2 (10.9)                                                             | 11.2                          |
| Krebs (2012) [99]                | DEWL          | Intensive Lifestyle Intervention (Diet) | Low-fat high-protein diet vs low-fat high-carbohydrate diet | 419               | 30                            | 58.0 (9.5)                                                             | 2.3                           |
| Azadbakht (2011) [100, 101]      | DASH          | Intensive Lifestyle Intervention (Diet) | “Dietary Approaches to Stop Hypertension” diet vs control diet (similar to Iranian dietary composition and pattern) | 31                | 44                            | 55.0 (6.5)                                                             | Not eligible                  |
| van Rooijen (2004) [102]         | -             | Intensive Lifestyle Intervention (Supervised Exercise Training) | Supervised and home-based aerobic exercise training vs supervised relaxation sessions | 149               | 40                            | 54.5 (NR)                                                              | Not eligible                  |
| First Author (year) [study ref.] | Trial Acronym | Study Category | Intervention and Comparator | Study Sample Size | Minimum Age Criterion (years) | Age of Recruited Population (years) Mean (SD) unless otherwise specified | Proportion Aged 18 to 39 years (%) |
|----------------------------------|---------------|----------------|-----------------------------|------------------|-------------------------------|---------------------------------------------------------------------------|---------------------------------|
| Sigal (2007) [103]               | DARE          | Intensive Lifestyle Intervention (Supervised Exercise Training) | Supervised aerobic vs resistance vs combined (aerobic-plus-resistance) exercise vs non-exercise control | 251              | 39                            | 54.2 (7.2)                                                               | 1.7                             |
| Church (2010) [104]              | HART-D        | Intensive Lifestyle Intervention (Supervised Exercise Training) | Supervised aerobic vs resistance vs combined (aerobic-plus-resistance) exercise training vs control (offered weekly stretching and/or relaxation sessions) | 262              | 30                            | 55.8 (8.7)                                                                    | 2.7                             |
| Balducci (2010) [105]            | IDES          | Intensive Lifestyle Intervention (Supervised Exercise Training) | Supervised combined (aerobic-plus-resistance) exercise training plus structured exercise counselling vs ongoing standard care | 606              | 40                            | 58.8 (8.6)                                                                     | Not eligible                     |
| Gordon (2008) [106]              | -             | Intensive Lifestyle Intervention (Supervised Exercise Training) | Yoga vs “conventional” (predominantly aerobic) exercise training vs ongoing standard care | 231              | 40                            | 63.8 (NR)                                                                      | Not eligible                     |
| Hegde (2011) [107]               | -             | Intensive Lifestyle Intervention (Supervised Exercise Training) | Yoga vs ongoing standard care | 123              | 40                            | 58.6 (9.4)                                                                     | Not eligible                     |

*In total, 1704 participants were recruited to UKPDS 34. 753 were randomised to the primary comparison of intensive glucose-lowering therapy with metformin vs conventional therapy. Secondary analyses compared participants in the metformin group versus individuals randomised to intensive glucose-lowering with chloropropamide, glibenclamide or insulin; a Median (IQR); c The BARI-2D study utilised a 2-by-2 factorial design; d >500 individuals were recruited but age data were only reported for n=488 that completed the 24-month follow-up visit.

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; DPP4i: dipeptidyl peptidase 4 inhibitor; DSMES: diabetes self-management education and support; GLP-1RA: glucagon-like peptide-1 receptor agonist; GLT: glucose-lowering therapy; HbA1c: glycated haemoglobin; IQR: interquartile range; NR: not reported; SD: standard deviation; SGLT2i: sodium-glucose cotransporter 2 inhibitor; TZD: thiazolidinedione.
**ESM Table 2 – Summary data for the Phase III research programmes of empagliflozin, liraglutide and sitagliptin**

|                | Number of trials | Total number of participants | Weighted mean age (years) | Range of mean ages (years) | Range of estimated proportions of individuals aged 18 to 39 years (%) | Estimated number of individuals aged 18 to 39 years | Combined proportion of individuals aged 18 to 39 years (%) |
|----------------|------------------|------------------------------|----------------------------|-----------------------------|--------------------------------------------------------------------|----------------------------------------------------|---------------------------------------------------------|
| **Empagliflozin** | 9                | 6,416                        | 57                        | 55 to 63                    | 0.2 to 7.3                                                          | 252                                                | 3.9                                                     |
| **Liraglutide**   | 7                | 5,121                        | 56                        | 53 to 58                    | 2.3 to 9.7                                                          | 237                                                | 4.6                                                     |
| **Sitagliptin**   | 12               | 7,437                        | 55                        | 51 to 69                    | 0.2 to 13.0                                                         | 435                                                | 5.9                                                     |

All trials allowed inclusion of adults aged ≥18 years, except one, which allowed those aged ≥21 years. All trials also reported age data as mean and standard deviation, thus allowing the estimation of the proportion of individuals aged 18-39 years.
**ESM Table 3 – Summary data for prominent trials of diabetes self-management education and support or intensive lifestyle interventions (diet or supervised exercise training) in type 2 diabetes**

|                                      | Number of trials | Total number of participants | Weighted mean age (years) | Range of mean ages (years) | Range of estimated proportions of individuals aged 18 to 39 years (%) | Estimated number of individuals aged 18 to 39 years | Combined proportion of individuals aged 18 to 39 years (%) |
|--------------------------------------|------------------|-----------------------------|---------------------------|----------------------------|---------------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------|
| **All trials reviewed**              |                  |                             |                           |                           |                                                                     |                                                     |                                                          |
| DSMES                                | 13               | 8,846                       | 60                        | 54 to 69                  |                                                                     |                                                     |                                                          |
| Diet                                 | 6                | 1,278                       | 56                        | 52 to 61                  |                                                                     |                                                     |                                                          |
| Supervised exercise training         | 6                | 1,622                       | 58                        | 54 to 64                  |                                                                     |                                                     |                                                          |
| **Trials in which individuals aged 18 to 39 years were eligible and where the relative proportion of these individuals could be estimated** |                  |                             |                           |                           |                                                                     |                                                     |                                                          |
| DSMES                                | 10               | 5,805                       | 60                        | 54 to 69                  | 0.01 to 4.9                                                         | 173                                                 | 3.0                                                      |
| Diet                                 | 5                | 1,247                       | 56                        | 52 to 61                  | 1.0 to 11.2                                                        | 43                                                  | 3.5                                                      |
| Supervised exercise training         | 2                | 513                         | 55                        | 54 to 56                  | 1.7 to 2.7                                                         | 11                                                  | 2.2                                                      |
ESM Figure 1 – Proportions of study populations aged between 18 and 39 years participating in cardio-renal outcomes trials

*analyses include only cardio-renal outcomes trials for which at least some individuals aged 18 to 39 years would be eligible. 23 further trials were identified that excluded individuals aged 18 to 39 years altogether (i.e. minimum age criterion ≥ 40 years), whilst two further trials did not report age as mean and standard deviation thus preventing estimation of the proportion of individuals aged 18 to 39 years.

*the BARI 2D trial also randomised individuals to insulin sensitising or insulin provision therapies. Readers are directed to the ESM Table 1 for full citations of included studies

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitor; GLT, Glucose-lowering therapy; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, thiazolidinedione; TZDM, type 2 diabetes mellitus
**ESM Figure 2 – Proportions of study populations aged between 18 and 39 years participating in Phase III trials of pharmacological glucose-lowering therapies**

**Phase III trials of pharmacological glucose-lowering therapies**

**Abbreviations:** DPP4i, dipeptidyl peptidase-4 inhibitor; GLT, Glucose-lowering therapy; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.
ESM Figure 3 – Proportions of study populations aged between 18 and 39 years participating in prominent trials examining the efficacy of diabetes self-management education and support or intensive lifestyle interventions in adult type 2 diabetes.

*Analyses include only trials for which at least some individuals aged 18 to 39 years would be eligible (i.e., minimum age criterion <40 years). A further six trials had minimum age criteria ≥40 years, thus excluding individuals aged 18 to 39 years altogether. Two further DSMES trials did not report standard deviation, thus preventing estimation of the proportion of individuals aged 18 to 39 years. 
*The Early Act trial specifically focused on dietary counselling with or without pedometer use to support increased physical activity.

Abbreviations: DSMES Diabetes self-management education and support.
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