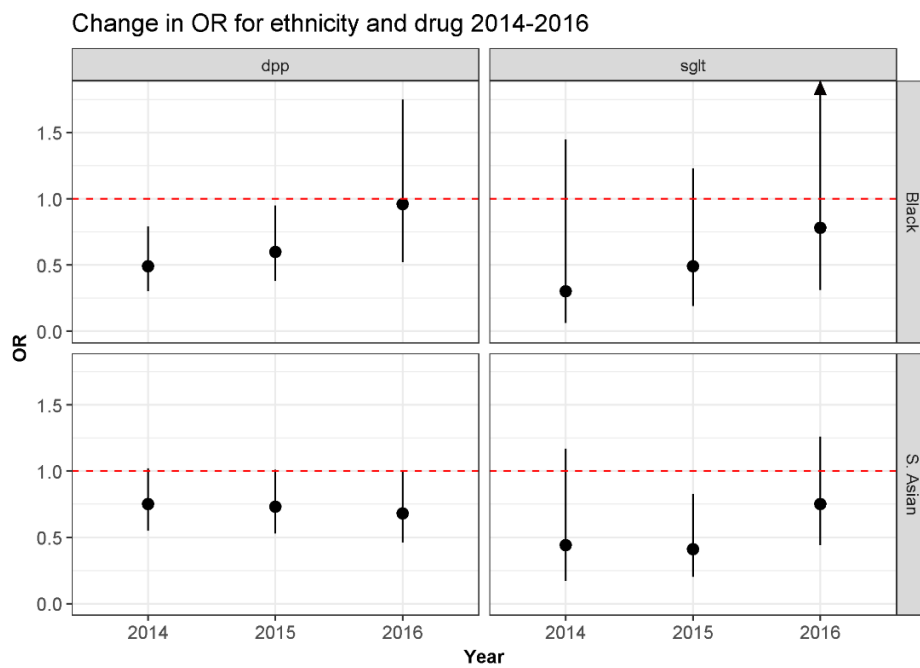


Supplementary Information: Factors associated with choice of intensification treatment for type 2 diabetes after metformin monotherapy: a cohort study in UK primary care

Drug	N	%
Insulin	368	34.0
TZDs	290	26.8
GLP1	286	26.45
SUs and DPP4is	55	5.1
Glinides	14	1.3
SU and insulin	14	1.3
DPP4i and insulin	11	1.0
Drug classes n<10	44	4.1
Total	1,082	

Supplementary Table 1: Drugs prescribed at first stage of intensification, other than the drug classes of interest.
Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, TZD: Thiazolidinediones, GLP1: Glucagon-like peptide-1



Supplementary Figure 1: Odds Ratios of the association between prescription for DPP4i and SGLT2i, and South Asian and Black ethnicity for 2014-2016 (excluding time as a covariate)

Variable		Insulin N=368	Other combinations n=714
Age category (years)	< 30	17 (4.6)	9 (1.3)
	30 to 39	43 (11.7)	45 (6.3)
	40 to 49	53 (14.4)	139 (19.5)
	50 to 59	74 (20.1)	224 (31.4)
	60 to 69	78 (21.2)	185 (25.9)
	70 to 79	63 (17.1)	88 (12.3)
	≥80	40 (10.9)	24 (3.4)
Gender	Female	175 (47.6)	321 (45)
BMI	Underweight/normal	59 (17.2)	47 (6.7)
	Overweight	102 (29.7)	132 (18.7)
	Obese	182 (53.1)	526 (74.6)
	Missing	25 (6.8)	9 (1.3)
Ethnicity	White	160 (82.1)	394 (90.6)
	South Asian	16 (8.2)	19 (4.4)
	Black	12 (6.2)	12 (2.8)
	Other	6 (3.1)	9 (2.1)
	Mixed	n <5	n <5
	Missing	173 (47)	279 (39.1)
Patient-level index of multiple deprivation	1 LEAST deprived	40 (20.6)	62 (17.2)
	2	36 (18.6)	64 (17.7)
	3	42 (21.6)	69 (19.1)
	4	37 (19.1)	86 (23.8)
	5 MOST deprived	39 (20.1)	80 (22.2)
	Missing	174 (47.3)	353 (49.4)
Alcohol status	Non-drinker	84 (25.7)	90 (13.1)
	Ex-drinker	42 (12.8)	92 (13.4)
	Current drinker	201 (61.4)	507 (73.6)
	Missing	41 (11.1)	25 (3.5)
Smoking status	Non-smoker	145 (40.1)	259 (36.3)
	Current	72 (19.9)	138 (19.4)
	Ex-smoker	145 (40.1)	316 (44.3)
	Missing	6 (1.6)	n <5
Day since first metformin prescription	Mean (SD)	561 (907)	1124 (1069)
HbA1c (mmol/mol)	Mean (SD)	85 (30)	77 (21)
	< 53 (7%)	29 (15.8)	45 (10.6)
	53 to 74	54 (29.5)	184 (43.2)
	>75 (9%)	100 (54.6)	197 (46.2)
	Missing	185 (50.3)	288 (40.3)
eGFR (ml/min/1.73m ²)	Mean (SD)	91 (24)	94 (19)
eGFR category (ml/min/1.73m ²)	< 60	27 (14.1)	40 (9.3)
	60 to 89	73 (38)	136 (31.7)
	≥ 90	92 (47.9)	253 (59)
	Missing	176 (47.8)	285 (39.9)
Proteinuric renal disease		7 (1.9)	14 (2)
Raised ACR		35 (35.4)	71 (23.5)
	Missing	269 (73.1)	412 (57.7)
Neuropathy		33 (9)	42 (5.9)
Amputation		5 (1.4)	11 (1.5)
Retinopathy		66 (17.9)	119 (16.7)
Blindness		n <5	8 (1.1)
>1 sign of microvascular disease		116 (31.5)	211 (29.6)
Systolic BP (mmHg)	Mean (SD)	130 (17)	134 (15)
	Missing	15 (4.1)	12 (1.7)
CVD		69 (18.8)	77 (10.8)
Heart failure		9 (2.4)	6 (0.8)
ACEi or ARB prescription		183 (49.7)	378 (52.9)
Statin prescription		212 (57.6)	502 (70.3)

Supplementary Table 2: Patient demographic and lifestyle factors for people prescribed insulin or other drug options at the first stage of intensification. Numbers are N (%) unless otherwise stated. **Abbreviations:** SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index, BP: Blood pressure, ACEi: Angiotensin-converting-enzyme inhibitor, ARB: Angiotensin II receptor blockers, SD: Standard Deviation, ACR: Albumin creatinine ratio

Variable	SU, Ref	DPP4i, OR (95% CI)	SGLT2i, OR (95% CI)
Age, years			
< 30	1	1.78 (1.03, 3.10)	3.55 (1.68, 7.51)
30-<40	1	1.07 (0.81, 1.41)	1.26 (0.80, 1.99)
40-<50	1	0.98 (0.83, 1.15)	1.42 (1.10, 1.83)
50-<60	1	1.01 (0.88, 1.15)	1.42 (1.15, 1.76)
60-<70	1	1	1
70-<80	1	1.00 (0.86, 1.16)	0.50 (0.36, 0.70)
80 +	1	0.83 (0.67, 1.03)	0.12 (0.04, 0.33)
Gender			
Male	1	1	1
Female	1	0.98 (0.88, 1.09)	1.03 (0.87, 1.22)
HbA1c (mmol/mol)			
< 54	1	1	1
54-75	1	1.27 (0.99, 1.64)	1.32 (0.80, 2.17)
75+	1	0.75 (0.5*, 0.98)	0.82 (0.50, 1.34)
eGFR (ml/min/1.73m²)			
< 60	1	1	1
60-89	1	1.10 (0.91, 1.32)	2.85 (1.53, 5.30)
90 +	1	1.12 (0.92, 1.37)	3.35 (1.80, 6.23)
Time taking metformin (years)			
< 1	1	1	1
1 to <3	1	1.22 (1.07, 1.39)	1.54 (1.23, 1.93)
> 3	1	1.25 (1.10, 1.42)	1.30 (1.04, 1.63)
Cardiovascular disease			
No CVD	1	1	1
CVD diagnosis	1	1.00 (0.87, 1.16)	0.95 (0.72, 1.27)
Retinopathy			
No retinopathy	1	1	1
Retinopathy diagnosis	1	1.12 (0.99, 1.28)	0.78 (0.60, 1.01)
BMI kg/m²			
Normal/underweight	1	1	1
Overweight	1	1.28 (1.08, 1.52)	1.95 (1.21, 3.14)
Obese	1	1.68 (1.43, 1.99)	4.98 (3.16, 7.83)
Smoking status			
None	1	1	1
Ex	1	1.01 (0.90, 1.12)	0.92 (0.76, 1.11)
Current	1	0.99 (0.85, 1.15)	0.78 (0.60, 1.01)
Ethnicity			
White	1	1	1
South Asian	1	0.73 (0.59, 0.89)	0.59 (0.40, 0.86)
Black	1	0.64 (0.48, 0.85)	0.45 (0.24, 0.82)
Other	1	0.66 (0.45, 0.97)	0.52 (0.25, 1.07)
Mixed	1	1.01 (0.48, 2.12)	0.73 (0.15, 3.60)
Patient-level IMD			
1 LEAST deprived	1	1	1
2	1	0.95 (0.80, 1.12)	0.98 (0.73, 1.30)
3	1	0.95 (0.80, 1.12)	1.02 (0.76, 1.33)
4	1	0.79 (0.67, 0.93)	0.61 (0.46, 0.81)
5 MOST	1	0.99 (0.84, 1.18)	0.59 (0.44, 0.80)
Calendar time			
Early 2014	1	1	1
Late 2014	1	1.18 (1.00, 1.38)	1.80 (1.24, 2.62)
Early 2015	1	1.38 (1.19, 1.60)	2.70 (1.92, 3.80)
Late 2015	1	1.66 (1.41, 1.95)	4.43 (3.14, 6.24)
Early 2016	1	2.17 (1.84, 2.57)	6.99 (4.99, 9.79)
Late 2016	1	2.56 (2.11, 3.10)	10.42 (7.33, 14.83)
Early 2017	1	2.85 (2.29, 3.54)	14.73 (10.23, 21.21)

Supplementary Table 3: Fully adjusted ORs (95% CIs) for prescription of DPP4i or SGLT2i compared with SUs using multinomial logistic regression with multiple imputation to account for missing data, also including adjustment for patient-level IMD (England only: N= 8,217).

Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index

Variable	SU, Ref N=2576	Sensitivity Analysis 1		Sensitivity Analysis 2	
		DPP4i, OR (95% CI) N=2137	SGLT2i, OR (95% CI) N=490	DPP4i, OR (95% CI) N=5285	SGLT2i, OR (95% CI) N=1488
Age, years					
< 30	1	1.94 (0.86, 4.35)	4.07 (1.42, 11.67)	1.36 (0.85, 2.17)	2.48 (1.39, 4.40)
30-<40	1	0.85 (0.59, 1.22)	1.48 (0.85, 2.56)	1.01 (0.81, 1.26)	1.32 (0.97, 1.81)
40-<50	1	0.94 (0.77, 1.16)	1.81 (1.31, 2.51)	0.98 (0.86, 1.11)	1.27 (1.04, 1.52)
50-<60	1	0.86 (0.72, 1.02)	1.53 (1.16, 2.03)	0.98 (0.88, 1.08)	1.21 (1.04, 1.42)
60-<70	1	1	1	1	1
70-<80	1	0.93 (0.77, 1.12)	0.56 (0.36, 0.87)	0.96 (0.85, 1.08)	0.47 (0.37, 0.60)
80 +	1	0.87 (0.67, 1.14)	0.14 (0.03, 0.60)	0.88 (0.74, 1.04)	0.14 (0.07, 0.28)
Gender					
Male	1	1	1	1	1
Female	1	0.94 (0.83, 1.07)	1.04 (0.84, 1.29)	0.92 (0.85, 1)	0.99 (0.87, 1.12)
HbA1c (mmol/mol)					
<= 53 (7%)	1	1	1	1	1
53-75	1	1.35 (1.02, 1.79)	1.11 (0.66, 1.89)	1.41 (1.14, 1.73)	1.17 (0.79, 1.71)
75+ (9%)	1	0.70 (0.53, 0.94)	0.78 (0.46, 1.32)	0.73 (0.59, 0.90)	0.79 (0.54, 1.16)
eGFR (ml/min/1.73m²)					
< 60	1	1	1	1	1
60-89	1	1.12 (0.91, 1.39)	15.45 (3.76, 63.37)	1.05 (0.90, 1.23)	5.88 (3.29, 10.50)
90 +	1	1.18 (0.93, 1.50)	16.52 (3.99, 68.29)	1.02 (0.86, 1.21)	6.77 (3.75, 12.23)
Time taking metformin (years)					
< 1	1	1	1	1	1
1 to <3	1	1.20 (1.01, 1.42)	1.48 (1.12, 1.95)	1.26 (1.13, 1.40)	1.40 (1.19, 1.64)
> 3	1	1.20 (1.02, 1.40)	1.24 (0.94, 1.64)	1.30 (1.17, 1.43)	1.23 (1.05, 1.44)
Cardiovascular disease (CVD)					
No CVD	1	1	1	1	1
CVD diagnosis	1	0.98 (0.83, 1.17)	0.76 (0.53, 1.09)	0.94 (0.84, 1.06)	0.95 (0.78, 1.16)
Retinopathy					
No retinopathy	1	1	1	1	1
Retinopathy diagnosis	1	0.97 (0.83, 1.14)	0.87 (0.64, 1.17)	1.09 (0.99, 1.21)	1.02 (0.86, 1.21)
BMI kg/m²					
Normal/underweight	1	1	1	1	1
Overweight	1	1.10 (0.88, 1.37)	2.48 (1.21, 5.07)	1.31 (1.14, 1.51)	2.22 (1.52, 3.26)
Obese	1	1.62 (1.31, 2.00)	6.01 (3.02, 11.99)	1.72 (1.50, 1.98)	5.66 (3.93, 8.17)
Smoking status					
None	1	1	1	1	1
Ex	1	0.96 (0.84, 1.10)	0.90 (0.71, 1.14)	0.98 (0.90, 1.07)	1.00 (0.87, 1.15)
Current	1	0.91 (0.76, 1.10)	0.76 (0.56, 1.03)	0.93 (0.83, 1.05)	0.80 (0.67, 0.96)
Ethnicity					
White	1	1	1	1	1
South Asian	1	0.72 (0.57, 0.92)	0.50 (0.31, 0.81)	0.70 (0.57, 0.86)	0.60 (0.42, 0.89)
Black	1	0.59 (0.41, 0.85)	0.45 (0.23, 0.91)	0.66 (0.49, 0.90)	0.55 (0.29, 1.06)
Other	1	0.92 (0.59, 1.43)	0.48 (0.18, 1.25)	0.78 (0.50, 1.24)	0.87 (0.40, 1.67)
Mixed	1	1.29 (0.53, 3.14)	0.36 (0.04, 3.00)	1.17 (0.55, 2.49)	2.05 (0.61, 6.91)
Calendar time					
Early 2014	1	1	1	1	1
Late 2014	1	1.19 (0.98, 1.45)	1.73 (1.07, 2.80)	1.13 (1.00, 1.29)	1.80 (1.37, 2.35)
Early 2015	1	1.37 (1.14, 1.65)	3.02 (1.97, 4.64)	1.35 (1.20, 1.53)	2.62 (2.04, 3.36)
Late 2015	1	1.72 (1.40, 2.11)	6.17 (4.02, 9.48)	1.58 (1.38, 1.80)	3.87 (3.01, 4.98)
Early 2016	1	2.31 (1.88, 2.86)	7.82 (5.09, 12.02)	2.00 (1.75, 2.29)	5.68 (4.43, 7.28)
Late 2016	1	2.35 (1.84, 2.99)	8.55 (5.41, 13.50)	2.17 (1.87, 2.52)	7.90 (6.12, 10.20)
Early 2017	1	2.90 (2.20, 3.82)	15.10 (9.41, 24.61)	2.44 (2.07, 2.88)	11.11 (8.53, 14.47)

Supplementary Table 4: Fully adjusted ORs (95% CIs) for prescription of DPP4i or SGLT2i compared with SUs in sensitivity analyses: 1. Using a complete case analysis approach. 2. Model included individuals that were censored or died in the 60 days after prescribing of the first intensification treatment, using multiple imputation to account for missing data. **Abbreviations:** SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated Glomerular Filtration Rate, BMI: Body mass index