

1 original article

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6 **Weight change in people with type 2 diabetes: secular trends**
7 **and the impact of alternative antihyperglycaemic drugs**
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16 **Aim:** This study aimed to describe the pattern of weight change in people with type 2 diabetes (T2DM) over time and when using alternative
17 treatment regimens.

18 **Methods:** Data were from routine clinical practice in the UK. The weight trend was determined for each year from 1995 to 2010 for both
19 prevalent and incident cases. Baseline weight was compared to absolute (mean Δ) and relative weights (% Δ) at 6, 12 and 24 months.

20 **Results:** Mean, standardized weight, in prevalent cases increased from 83.4 to 92.1 kg for males and from 73.5 to 79.9 kg for females
21 between 1995 and 2010 ($p < 0.0001$). For incident cases, the respective figures were 86.7 to 93.6 kg for males and 76.0 to 80.7 kg ($p <$
22 0.0001) for females. Between baseline and 6, 12 and 24 months, there were significant changes in weight for the majority of the treatment
23 regimens selected for analysis. The largest weight increase at 12 months was for the patients who were prescribed a combination therapy with
24 insulin and a thiazolidinedione, with a median increase of 4.1 kg (95% CI -0.60 to 8.0 , $p < 0.001$). The largest weight decrease at 12 months
25 was for the patients who were prescribed a combination therapy of metformin and exenatide, with a median decrease of -7.0 kg (95% CI
26 -12.0 to -2.0 , $p < 0.001$).

27 **Conclusions:** There was a continual increase in body weight in people with T2DM over time, and considerable differences in the impact on
28 weight using alternative treatment regimens. At the same time, glycaemic control remained relatively unchanged.

29 **Keywords:** antidiabetic drugs, obesity, secular trends, type 2 diabetes, weight change

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35 **Introduction**

36 Type 2 diabetes (T2DM) is a chronic condition characterized by
37 excess micro- and macrovascular morbidity and mortality [1].
38 Hyperglycaemia is a risk factor for these complications and,
39 therefore, the attainment of near-normal glycaemia is a
40 major therapeutic target for people with the disease [2]. The
41 benefits of sustained glycaemic control have been shown
42 in the United Kingdom Prospective Diabetes Study, which
43 found that a 0.9% decrease in haemoglobin A1c (HbA1c)
44 in the intensive treatment group, was associated with a 25%
45 reduction in microvascular complications when compared with
46 conventional treatment [3].

47
48 Where lifestyle modification has failed to result in
49 appropriate glycaemic control, metformin is now universally
50 recommended as the first-line treatment for patients with
51 T2DM. However, therapy failure occurs within 3 years in over
52 40% of patients on metformin alone [4], resulting in the need
53 for multiple oral antidiabetes agents (OADs) and, eventually,
54 insulin.

35 Pharmacotherapy aiming at normal glycaemia may be asso-
36 ciated with an increased risk of hypoglycaemia and weight
37 gain. Increasing weight is of particular concern because more
38 than 80% of the T2DM population are overweight or obese
39 at diagnosis [5], set against a background of increasing obe-
40 sity in the general population [6,7]. For people with diabetes,
41 obesity may not only increase cardiovascular risk but may also
42 have a detrimental impact on health-related quality of life,
43 treatment adherence and treatment cost-effectiveness [8,9].
44 Many glucose-lowering therapies, including insulin, sulpho-
45 nylurea and the thiazolidinediones [(TZDs), or glitazones],
46 are associated with weight gain [8–11]. Conversely, metformin
47 and the newer, incretin-mimetic therapies—the GLP-1 ana-
48 logues (exenatide and liraglutide) [12] and the dipeptidyl
49 peptidase (DPP)-4 inhibitors (sitagliptin, vildagliptin and
50 saxagliptin) [13]—are associated with weight loss or weight
51 neutrality, which may translate into improved outcomes [9,14].

52 In this study, we aimed to characterize the secular weight
53 pattern for people with T2DM and, in particular, to evaluate
54 weight change associated with different diabetes treatment
55 regimens, using data from routine clinical practice. In
56 order to place these data in the context of corresponding
57 clinical outcome, we also characterized the pattern of glucose
58 control (HbA1c) in relation to body weight changes as a

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1 function of different glucose-lowering therapeutic regimens.
2 For completeness, we also include reference weight data from
3 the non-diabetic population.

4 **Methods**

5 **Ethics Statement**

6 The General Practice Research Database Group has obtained
7 ethical approval from a multicentre research ethics committee
8 for all observational research that does not involve patient
9 involvement. Approval for this particular study was awarded
10 by its Independent Scientific Advisory Committee, reference
11 11_004.

12 **Data Source**

13 Data were extracted from the General Practice Research
14 Database (GPRD) [15], a longitudinal, anonymized data set
15 derived from over 350 primary care practices in the UK.
16 It contains records for approximately 10 million patients,
17 of whom approximately 5 million are actively registered.
18 Available data include patient demographics, medical history,
19 test results and prescriptions. Ethnicity is not recorded for
20 individual patients and is therefore not included in our study.
21 Diagnostic information in GPRD is recorded using the Read
22 Code classification.

23 **Patient Selection and Coding of Diabetes Type**

24 All patients included in the cohort were registered with a
25 general practice contributing to the GPRD dataset. Patients
26 were extracted with a Read Code indicative of diabetes. As not
27 all Read Codes for diabetes differentiate between type 1 and
28 type 2, and some patient histories may erroneously contain
29 codes for both types, patients with T2DM were defined by one
30 or more of the following:

- 31 1. Read Codes exclusively indicative of T2DM
- 32 2. Prescription of two classes of OAD
- 33 3. A Read Code indicative of T2DM (regardless of others
34 indicative of type 1 or non-specific diabetes) and a
35 prescription for an OAD

36 Patients were defined as incident cases if they had a minimum
37 of 180 days between registration at the practice and their
38 presentation with diabetes, defined as the earlier of first
39 diagnosis or first prescription of a diabetes medication.

40 **Baseline Characteristics**

41 Baseline date was defined as that on which the treatment
42 regimen was initiated. Baseline weight was defined as the
43 nearest weight measurement recorded prior to baseline date
44 to a maximum of -180 days. Other baseline characteristics
45 (HbA1c, systolic and diastolic blood pressure, cholesterol,
46 high density lipids, low density lipids and triglycerides) were
47 determined as the value nearest to baseline in the preceding
48 30 days. If no value was recorded, the nearest value to baseline
49 in the subsequent 30 days was recorded. If again no value was
50 recorded, the nearest value in the year prior to baseline was
51 used.

52 **Secular Trends in Weight**

53 The secular trend of weight was analysed for patients with and
54 without T2DM and plotted for each year from 1995 to 2010,
55 inclusively. The first weight value recorded per patient per year
56 was used. Annual mean weights were standardized by age to
57 the population profile for 2010 and presented by sex. Age- and
58 sex-specific weight profiles were also calculated for 2000 and
59 2010.

60 **Diabetes-specific Treatment Regimens**

61 Treatments were considered in the following categories: (i)
62 exenatide, (ii) DPP-4 inhibitors, (iii) insulin, (iv) metformin,
63 (v) TZDs, (vi) sulphonylurea and (vii) other OADs.

64 Patients were defined by treatment cohorts based on the
65 criteria of a minimum duration of 180 days on the same
66 therapy combination and a "wash-in" period of at least 90 days
67 between the patients' registering at the practice and their first
68 relevant prescription.

69 **Outcome Measurement**

70 Weight change was measured from baseline to 6, 12 and
71 24 months (± 90 days) both as an absolute change in kilograms
72 and as percentage change, and compared using the Wilcoxon
73 signed rank test. For specific regimens, a rolling 30-day average
74 weight, indexed to baseline, was presented. We also evaluated
75 the mean HbA1c for a limited number of regimens by year, for
76 the study period.

77 **Results**

78 **Secular Trends in Weight**

79 For patients with T2DM, 1 822 790 weight measurements were
80 included in the secular trend analysis, ranging from 38 408
81 in 1995 to 184 474 in 2010. For the prevalent cohort, mean
82 standardized weight increased from 83.4 to 92.1 kg for males
83 and from 73.5 to 79.9 kg for females (figure 1). For incident
84 cases, the figures were 86.7 to 93.6 kg for males and 76.0 to
85 80.7 kg for females.

86 For reference purposes, for the population as a whole aged
87 ≥ 35 years, corresponding data were available for 4 088 482
88 people without diabetes. Here, mean standardized weight
89 increased over the study period from 80.3 to 86.7 kg for males
90 and from 67.2 to 72.5 kg for females (figure 1).

91 **Study Subjects and Baseline Characteristics**

92 Baseline characteristics for the T2DM cohorts in 2000 and
93 2010, presented by 2010 weight quartiles, are shown in Table 1.
94 In both cohorts, mean age was lower in relation to increasing
95 weight, while there was a slight increase in mean HbA1c.
96 Comparison between the cohorts showed an improved profile
97 in 2010 in terms of HbA1c, total cholesterol, lipids and blood
98 pressure.

99 There were 32 therapy regimens with frequencies greater
100 than 100. The total number of valid therapy periods was
101 240 307. Of these patients, 149 004 (62.0%), 133 298 (55.5%)

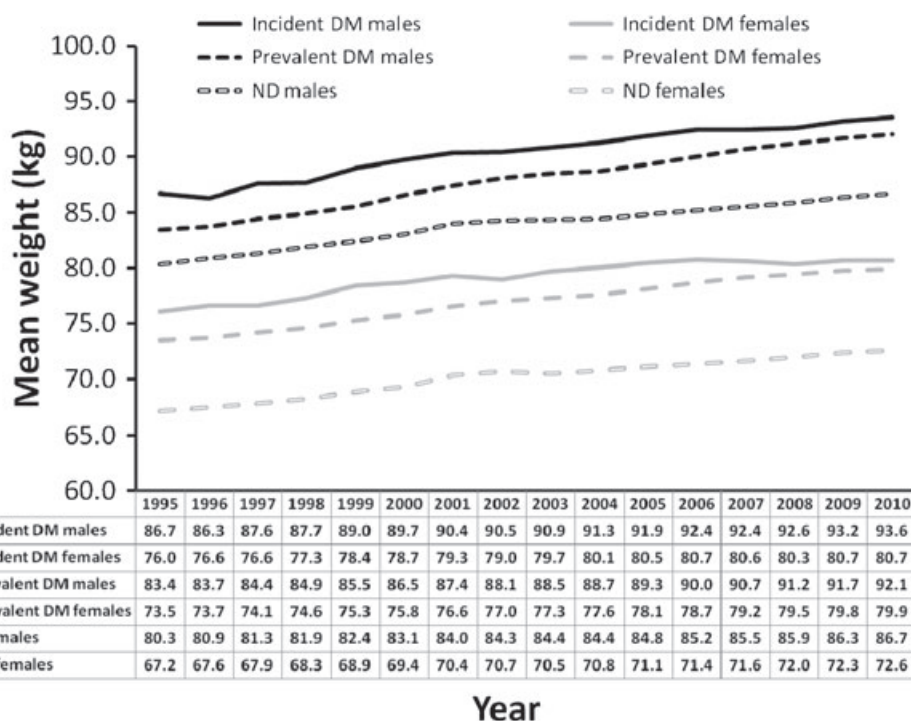


Figure 1. Secular trend for age-standardized, mean weight for people with prevalent and incident diabetes and for people without diabetes. DM, diabetes mellitus; ND, non-diabetic.

Table 1. Baseline characteristics by weight quartile of patients with diabetes in 2000 and 2010.

Year	2000				2010			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
n	21 860	—	19 923	—	16 914	11 495	—	—
Age—years (s.d.)	67.3 (15.2)	64.8 (13.3)	62.1 (12.2)	57.2 (11.9)	69.9 (14.3)	66.9 (12.8)	64.2 (12.1)	59.9 (11.4)
Females—%	67.1	39.8	32.5	28.7	68.1	43.8	33.4	29.3
Systolic BP—mmHg (s.d.)	143.9 (22.6)	145.2 (20.9)	146.0 (20.0)	147.0 (19.4)	134.7 (19.0)	136.2 (17.6)	136.8 (17.0)	138.1 (16.8)
Diastolic BP—mmHg (s.d.)	78.6 (10.6)	80.7 (10.4)	82.7 (10.4)	85.4 (10.5)	74.0 (10.5)	76.0 (10.3)	77.5 (10.3)	79.9 (10.5)
HbA1c—% (s.d.)	7.9 (1.9)	7.9 (1.8)	8.0 (1.8)	8.1 (1.8)	7.2 (1.6)	7.4 (1.6)	7.4 (1.6)	7.6 (1.7)
Total cholesterol—mmol/l (s.d.)	5.4 (1.2)	5.4 (1.1)	5.3 (1.1)	5.3 (1.1)	4.5 (1.1)	4.3 (1.1)	4.3 (1.1)	4.3 (1.1)
HDL—mmol/l (s.d.)	3.2 (1.0)	3.2 (0.9)	3.2 (0.9)	3.1 (0.9)	2.4 (0.9)	2.4 (0.9)	2.4 (0.9)	2.3 (0.9)
LDL—mmol/l (s.d.)	1.4 (0.5)	1.3 (0.4)	1.2 (0.3)	1.1 (0.3)	1.4 (0.4)	1.3 (0.4)	1.2 (0.4)	1.1 (0.3)
Triglycerides—mmol/l (s.d.)	1.9 (1.1)	2.1 (1.2)	2.4 (1.2)	2.6 (1.3)	1.5 (0.8)	1.7 (0.9)	1.8 (1.0)	2.0 (1.0)
GP contacts preceding year—mean n (s.d.)	11.3 (9.7)	11.0 (9.4)	11.1 (9.5)	11.3 (10.2)	15.0 (12.8)	14.3 (12.0)	14.1 (11.7)	14.7 (12.4)

BP, blood pressure; GP, general practice; HbA1c, haemoglobin A1c; s.d., standard deviation.

*Quartiles in 2010—Q1: ≤ 72.0.3 kg; Q2: > 72.0.3 ≤ 81.0; Q3: > 84.1 ≤ 98.0; Q4: > 98.0.

and 85 925 (35.8%) had weight measurements at circa 180, 365 and 730 days, respectively. The most common regimen was metformin monotherapy with 80 160 observations. Baseline characteristics by regimen are shown in Table 2.

Absolute Weight Change

Absolute changes in weight for the 32 therapy combinations at 6, 12 and 24 months are shown in Table 3. At each time point, there were significant changes in weight for the

majority of regimens. For the patients who were prescribed the most common regimen, metformin monotherapy, there was a median average reduction in weight of −1.0 kg [inter-quartile range (IQR) −4.1 to 1.6 kg, $p < 0.001$] at 6 months, −1.1 kg (IQR −4.6 to 2.0 kg, $p < 0.001$) at 12 months and −1.5 kg (IQR −5.0 to 2.0 kg, $p < 0.001$) at 24 months. Insulin monotherapy was associated with an average weight gain of 2.1 kg (IQR −0.9 to 5.9 kg, $p < 0.001$) at 6 months, 3.4 kg (IQR 0.0 to 7.6 kg, $p < 0.001$) at 12 months and 4.5 kg (IQR 0.0 to 9.0 kg, $p < 0.001$) at 24 months.

Table 2. Mean (s.d.) characteristics of patients with type 2 diabetes at baseline by treatment regimen.

Treatment regimen	n	Weight (kg)	Age (years)	Blood pressure systolic + diastolic (mmHg)	HbA1c (%)	Cholesterol (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	Triglycerides (mmol/L)
Met	80	90.72 (18.93)	60.46 (12.61)	139.70 (17.98)	80.92 (10.49)	5.02 (1.25)	1.20 (0.34)	2.79 (0.99)	2.20 (1.18)
Met Sulph	50	86.09 (18.41)	62.21 (12.09)	139.92 (18.47)	79.90 (10.21)	4.74 (1.20)	1.19 (0.35)	2.48 (0.90)	2.15 (1.18)
Sulph	38	77.85 (16.43)	66.46 (12.46)	142.20 (20.68)	79.71 (11.12)	5.12 (1.34)	1.24 (0.38)	2.75 (1.04)	2.12 (1.18)
Ins	13	82.00 (18.60)	63.18 (13.28)	138.24 (20.62)	76.64 (11.02)	4.73 (1.29)	1.22 (0.40)	2.46 (0.93)	2.10 (1.22)
Met TZD	12	93.73 (19.44)	58.43 (11.38)	137.67 (16.34)	80.05 (9.66)	4.56 (1.11)	1.19 (0.33)	2.41 (0.87)	2.19 (1.17)
Met Sulph TZD	10	89.64 (19.32)	60.58 (11.20)	137.07 (16.30)	78.28 (9.50)	4.33 (1.02)	1.17 (0.34)	2.28 (0.77)	2.06 (1.15)
Met Ins	10	90.02 (18.66)	59.94 (11.52)	138.33 (17.77)	78.09 (10.16)	4.56 (1.17)	1.19 (0.36)	2.37 (0.86)	2.16 (1.24)
Sulph TZD	42	82.17 (17.63)	67.33 (11.53)	140.05 (18.52)	76.95 (10.36)	4.65 (1.10)	1.22 (0.36)	2.50 (0.88)	2.10 (1.12)
Met Sulph Ins	27	89.73 (18.70)	60.88 (11.55)	137.02 (17.20)	77.91 (9.87)	4.36 (1.09)	1.14 (0.33)	2.28 (0.82)	2.14 (1.19)
Met Sulph DPP-4	22	92.38 (19.58)	61.89 (11.05)	135.10 (15.03)	77.22 (9.22)	4.08 (0.91)	1.13 (0.33)	2.12 (0.74)	1.98 (1.05)
Met Sulph Other_OAD	19	87.28 (20.19)	61.98 (11.13)	143.66 (19.02)	80.62 (9.99)	4.93 (1.22)	1.15 (0.35)	2.47 (1.00)	2.23 (1.21)
Met DPP-4	19	96.74 (20.68)	58.67 (11.14)	135.11 (15.12)	78.69 (9.54)	4.31 (1.03)	1.17 (0.37)	2.27 (0.81)	2.06 (1.09)
Met Other_OAD	14	91.93 (19.87)	58.33 (11.26)	140.22 (17.95)	80.68 (10.42)	4.84 (1.17)	1.18 (0.34)	2.52 (0.94)	2.28 (1.30)
TZD	14	86.83 (18.69)	65.31 (11.94)	137.41 (17.57)	76.98 (10.75)	4.64 (1.11)	1.25 (0.36)	2.56 (0.94)	2.06 (1.06)
Sulph Ins	13	84.06 (18.65)	68.41 (11.67)	137.27 (19.82)	75.06 (10.85)	4.43 (1.19)	1.18 (0.39)	2.32 (0.88)	2.17 (1.21)
Sulph Other_OAD	8	80.18 (17.20)	65.75 (11.37)	143.06 (19.59)	79.73 (10.22)	5.28 (1.34)	1.18 (0.40)	2.66 (0.94)	2.34 (1.33)
Other_OAD	7	83.09 (17.62)	63.21 (13.38)	140.84 (19.10)	80.01 (11.22)	5.01 (1.27)	1.21 (0.39)	2.66 (0.95)	2.15 (1.17)
Met Sulph Exen	6	110.91 (19.03)	55.78 (10.00)	136.44 (15.71)	79.30 (9.49)	4.08 (0.94)	1.05 (0.31)	2.10 (0.71)	2.28 (1.20)
Met Ins TZD	5	98.62 (19.89)	56.58 (11.48)	136.32 (16.64)	77.35 (9.85)	4.42 (1.11)	1.12 (0.30)	2.31 (0.78)	2.33 (1.29)
Met TZD Other_OAD	3	95.37 (22.11)	58.03 (10.88)	137.38 (17.75)	78.66 (9.88)	4.60 (1.10)	1.23 (0.35)	2.34 (0.80)	2.16 (1.22)
Met Exen	3	112.22 (20.58)	53.14 (10.39)	133.75 (14.64)	79.41 (10.08)	4.42 (1.10)	1.11 (0.30)	2.35 (0.90)	2.20 (1.15)
Sulph DPP-4	3	86.61 (19.44)	69.04 (11.16)	135.86 (16.21)	74.95 (10.21)	4.33 (1.08)	1.17 (0.33)	2.34 (0.88)	2.01 (1.09)
Met TZD DPP-4	2	99.72 (21.17)	58.21 (10.78)	134.74 (15.35)	76.99 (9.54)	4.22 (0.92)	1.18 (0.36)	2.16 (0.72)	2.01 (1.05)
Ins TZD	2	95.96 (17.29)	61.67 (12.24)	137.65 (16.56)	74.94 (10.93)	4.53 (1.31)	1.12 (0.31)	2.45 (1.03)	2.45 (1.43)
Met Ins Exen	2	109.71 (18.63)	57.05 (9.49)	135.71 (15.91)	76.62 (10.03)	4.10 (1.08)	1.10 (0.39)	2.11 (0.81)	2.42 (1.30)
Met Ins Other_OAD	2	97.79 (21.91)	58.54 (10.69)	135.89 (17.86)	76.89 (10.22)	4.43 (1.05)	1.14 (0.29)	2.19 (0.74)	2.31 (1.25)
Met Sulph TZD Other_OAD	2	92.83 (21.12)	61.30 (9.79)	139.50 (16.00)	78.11 (9.45)	4.46 (1.03)	1.16 (0.31)	2.20 (0.73)	2.11 (1.19)
Met Sulph TZD DPP-4	1	91.68 (19.23)	59.91 (10.93)	134.59 (15.55)	76.34 (9.29)	4.19 (1.07)	1.18 (0.38)	2.17 (0.83)	1.93 (1.17)
Met Sulph Ins TZD	1	92.90 (20.53)	57.96 (10.97)	135.90 (16.57)	77.92 (10.07)	4.52 (1.46)	1.17 (0.32)	2.27 (0.78)	2.13 (1.27)
Ins Other_OAD	1	90.96 (19.12)	63.43 (12.74)	138.47 (20.60)	77.45 (10.96)	4.63 (1.31)	1.21 (0.38)	2.15 (0.83)	2.35 (1.37)
Sulph TZD Other_OAD	1	86.43 (19.30)	67.09 (10.27)	139.86 (16.30)	76.66 (9.26)	4.63 (1.06)	1.19 (0.33)	2.49 (0.81)	2.19 (1.01)
DPP-4	1	87.34 (20.52)	67.19 (12.30)	135.79 (15.41)	77.73 (9.91)	4.71 (0.98)	1.25 (0.38)	2.62 (0.88)	2.16 (1.23)

DPP, dipeptidyl peptidase; HbA1c, haemoglobin A1c; OAD, oral antidiabetes agents; s.d., standard deviation; TZD, thiazolidinedione.

Table 3. Absolute and relative mean change in weight from baseline by treatment regimen—in kilograms (% change).

Treatment regimen	6 months				12 months				24 months						
	n	Median	IQR	p	n	Median	IQR	p	n	Median	IQR	p			
Met	50 839	-1.00 (-1.34)	-4.08 (-4.70)	1.60 (1.80)	0.000 (0.000)	46 137	-1.10 (-1.39)	-4.60 (-5.17)	2.00 (2.24)	0.000 (0.000)	29 487	-1.50 (-1.64)	-5.00 (-5.77)	2.00 (2.54)	0.000 (0.000)
Met Sulph	30 840	0.50 (0.56)	-2.09 (-2.64)	3.30 (4.00)	0.000 (0.000)	27 950	1.00 (1.03)	-2.00 (-2.60)	4.00 (4.75)	0.000 (0.000)	18 134	1.00 (1.05)	-2.50 (-2.94)	4.50 (5.36)	0.000 (0.000)
Sulph	22 031	1.00 (1.38)	-2.00 (-2.47)	4.10 (5.56)	0.000 (0.000)	20 161	1.50 (1.94)	-1.80 (-2.20)	5.00 (6.43)	0.000 (0.000)	13 715	1.60 (2.11)	-2.00 (-2.42)	5.40 (7.11)	0.000 (0.000)
Met TZD	8 482	1.36 (1.45)	-1.50 (-1.69)	4.50 (4.89)	0.000 (0.000)	7 723	2.01 (2.48)	-1.00 (-1.28)	5.50 (6.10)	0.000 (0.000)	5 198	2.80 (3.03)	-1.00 (-1.07)	6.60 (7.18)	0.000 (0.000)
Insul	7 603	2.10 (2.74)	-0.88 (-0.98)	5.90 (7.50)	0.000 (0.000)	6 833	3.40 (4.24)	0.00 (0.00)	7.57 (9.68)	0.000 (0.000)	4 903	4.50 (5.56)	0.00 (0.00)	9.00 (11.54)	0.000 (0.000)
Met Sulph TZD	7 237	1.80 (1.96)	-1.00 (-1.05)	4.60 (5.19)	0.000 (0.000)	6 504	2.50 (2.88)	-0.11 (-0.15)	5.90 (6.45)	0.000 (0.000)	4 013	3.40 (3.98)	0.00 (0.00)	7.00 (7.87)	0.000 (0.000)
Met Insul	6 723	1.00 (1.22)	-1.73 (-1.90)	4.08 (4.82)	0.000 (0.000)	6 052	1.80 (1.93)	-1.30 (-1.50)	5.40 (6.13)	0.000 (0.000)	4 378	2.40 (2.78)	-1.00 (-1.08)	6.35 (7.39)	0.000 (0.000)
Sulph TZD	2 699	2.00 (2.53)	-0.50 (-0.60)	5.00 (6.06)	0.000 (0.000)	2 490	3.00 (3.77)	0.00 (0.00)	6.35 (7.79)	0.000 (0.000)	1 581	3.73 (4.69)	0.00 (0.00)	7.40 (9.41)	0.000 (0.000)
Met Sulph Insul	1 808	1.50 (1.67)	-1.00 (-1.31)	4.59 (5.22)	0.000 (0.000)	1 520	2.19 (2.54)	-0.92 (-1.00)	5.50 (6.19)	0.000 (0.000)	8 58	2.61 (3.04)	-0.70 (-0.71)	6.11 (7.15)	0.000 (0.000)
Met Sulph DPP-4	1 555	-0.50 (-0.61)	-2.70 (-2.86)	1.50 (1.64)	0.000 (0.000)	976	-0.90 (-0.90)	-3.10 (-3.53)	1.42 (1.70)	0.000 (0.000)	148	-1.13 (-1.39)	-4.00 (-4.25)	1.73 (2.00)	0.000 (0.001)
Met DPP-4	1 304	-1.00 (-1.18)	-3.70 (-3.89)	1.00 (1.17)	0.000 (0.000)	810	-1.12 (-1.46)	-4.50 (-4.55)	1.00 (1.25)	0.000 (0.000)	158	-1.19 (-1.28)	-6.00 (-6.26)	1.00 (1.01)	0.000 (0.000)
Met Sulph Other_OAD	1 183	0.00 (0.00)	-3.20 (-3.84)	3.00 (3.51)	0.481 (0.533)	975	0.11 (0.15)	-3.50 (-3.45)	4.54 (5.26)	0.000 (0.000)	614	0.77 (0.90)	-3.00 (-3.58)	6.03 (7.16)	0.000 (0.000)
Met Other_OAD	963	-0.50 (-0.62)	-4.00 (-3.96)	2.90 (3.32)	0.018 (0.035)	778	0.54 (0.58)	-3.00 (-3.45)	4.40 (4.98)	0.011 (0.005)	494	0.90 (0.89)	-3.00 (-3.45)	5.01 (5.99)	0.002 (0.001)
TZD	940	1.80 (1.97)	-1.00 (-1.11)	5.00 (5.88)	0.000 (0.000)	823	2.50 (2.89)	-1.00 (-1.22)	6.00 (6.96)	0.000 (0.000)	530	3.42 (3.81)	-0.63 (-0.93)	7.70 (9.25)	0.000 (0.000)
Sulph Insul	843	2.00 (2.41)	-1.00 (-1.10)	5.00 (6.06)	0.000 (0.000)	704	2.68 (3.04)	-0.80 (-0.93)	5.98 (7.07)	0.000 (0.000)	377	3.20 (3.78)	-0.61 (-0.81)	6.75 (8.48)	0.000 (0.000)
Met Sulph Exen	512	-3.80 (-3.32)	-7.10 (-6.47)	-0.90 (-0.82)	0.000 (0.000)	331	-5.30 (-5.13)	-9.50 (-8.40)	-1.70 (-1.38)	0.000 (0.000)	79	-6.50 (-5.91)	-11.70 (-9.95)	-1.00 (-1.19)	0.000 (0.000)
Sulph Other_OAD	502	0.00 (0.00)	-3.23 (-3.99)	3.00 (3.68)	0.722 (0.815)	409	0.67 (0.94)	-2.73 (-3.30)	4.09 (5.19)	0.009 (0.006)	281	0.90 (1.25)	-3.09 (-4.14)	5.36 (7.02)	0.004 (0.004)
Other_OAD	438	0.00 (0.00)	-3.00 (-3.84)	3.62 (4.51)	0.167 (0.136)	374	0.19 (0.20)	-3.00 (-3.74)	4.00 (4.88)	0.188 (0.116)	247	0.30 (0.32)	-3.18 (-4.22)	4.08 (5.05)	0.319 (0.353)
Met Insul TZD	362	2.39 (2.82)	-1.00 (-0.99)	6.00 (5.66)	0.000 (0.000)	277	4.00 (3.95)	0.00 (0.00)	7.86 (8.15)	0.000 (0.000)	138	4.00 (4.21)	-1.00 (-1.09)	10.00 (10.12)	0.000 (0.000)
Met Exen	304	-4.75 (-4.28)	-8.50 (-7.80)	-1.00 (-1.05)	0.000 (0.000)	171	-6.99 (-6.11)	-12.00 (-10.93)	-2.00 (-1.82)	0.000 (0.000)	39	-8.70 (-7.81)	-12.50 (-11.42)	-2.90 (-2.23)	0.000 (0.000)

Table 3. Continued.

Treatment regimen	6 months			12 months			24 months					
	n	Median	IQR	p	n	Median	IQR	p	n	Median	IQR	p
Met TZD Other_OAD	247	1.00 (1.19)	-2.00 (-1.92)	4.45 (4.84)	1.60 (1.82)	5.87 (6.24)	-1.98 (-1.72)	0.000 (0.000)	141	2.69 (3.49)	-0.56 (-0.61)	0.000 (0.000)
Sulph DPP-4	238	0.00	-2.50	2.00	0.00	2.00	-2.50	0.588 (0.782)	19	0.70 (0.92)	-4.60 (-7.14)	0.687 (0.687)
Met TZD DPP-4	194	-0.70 (-0.68)	-3.50 (-3.43)	2.01 (2.24)	0.021 (0.026)	3.05 (3.05)	-3.05 (-3.15)	0.695 (0.634)	20	3.20 (4.13)	0.06 (0.07)	0.010 (0.014)
Met Insul Exen	181	-5.00 (-4.54)	-8.65 (-8.12)	-0.80 (-0.73)	0.000 (0.000)	-0.30 (-0.29)	-9.98 (-9.74)	0.000 (0.000)	16	-4.30 (-3.83)	-7.60 (-8.43)	0.023 (0.026)
Met Insul Other_OAD	173	0.00 (0.00)	-3.30 (-3.44)	3.01 (2.96)	0.595 (0.771)	4.10 (4.91)	-2.05 (-2.19)	0.086 (0.037)	62	3.20 (3.54)	-0.10 (-0.14)	0.000 (0.000)
Insul TZD	168	2.30 (2.28)	-1.27 (-1.36)	5.43 (6.20)	0.000 (0.000)	8.00 (8.40)	-0.60 (-0.73)	0.000 (0.000)	78	4.77 (5.60)	0.60 (0.66)	0.000 (0.000)
Met Sulph TZD	141	0.40	-2.39	3.82	0.113	5.00	-1.50	0.005	68	2.00	-2.22	0.040
Other_OAD	125	0.58 (0.58)	-2.71 (-2.71)	3.93 (3.93)	0.134 (0.134)	5.03 (5.03)	-2.05 (-2.05)	0.004 (0.004)	35	6.00 (6.25)	2.00 (2.44)	0.000 (0.000)
Met Sulph Insul TZD	112	1.00 (1.05)	-1.29 (-1.40)	3.08 (3.81)	0.005 (0.005)	3.70 (4.31)	-1.60 (-1.87)	0.024 (0.022)	22	1.70 (1.78)	-1.66 (-1.64)	0.322 (0.289)
DPP-4	98	0.40 (0.42)	-2.78 (-3.03)	4.60 (4.69)	0.123 (0.112)	7.90 (7.81)	-1.50 (-2.10)	0.009 (0.007)	43	5.10 (5.45)	0.70 (1.00)	0.000 (0.000)
Insul Other_OAD	80	1.51 (1.60)	-1.48 (-1.68)	4.96 (5.73)	0.006 (0.005)	5.93 (6.82)	-0.24 (-0.27)	0.000 (0.000)	41	2.45 (2.96)	-2.75 (-3.22)	0.043 (0.030)
Sulph TZD	79	-0.90 (-0.82)	-3.63 (-4.05)	1.70 (2.41)	0.031 (0.034)	1.05 (1.54)	-3.95 (-5.13)	0.043 (0.036)	8	-0.60 (-0.83)	-2.65 (-2.76)	0.575 (0.674)

DPP, Dipeptidyl peptidase; IQR, inter-quartile range; OAD, oral antidiabetes agents; TZD, thiazolidinedione.

1 At 6 months, the largest weight increase was associated with
2 the patients who were prescribed a combination therapy of
3 metformin, insulin, sulphonylurea and TZDs, with a median
4 increase of 2.6 kg (IQR -0.25 to 6.0 kg, $p < 0.001$). The largest
5 reduction was for the patients who were prescribed metformin,
6 insulin and exenatide, with a median reduction of -5.0 kg
7 (IQR -8.65 to -0.8 kg, $p < 0.001$).

8 The largest weight increase at 12 months was for the patients
9 who were prescribed a combination therapy of insulin and TZD,
10 with a median increase of 4.1 kg (IQR -0.60 to 8.0 kg, $p <$
11 0.001). The largest weight decrease at 12 months was associated
12 with the patients who were prescribed a combination therapy
13 of metformin and exenatide, with a median decrease of -7.0 kg
14 (IQR -12.0 to -2.0 kg, $p < 0.001$).

15 At 24 months, the largest weight increase was for patients
16 treated with metformin, insulin, sulphonylurea and TZD, with
17 an increase of 6.0 kg (IQR 2.0 to 9.6 kg, $p < 0.001$). The largest
18 decrease was for patients treated with metformin and exenatide:
19 -8.7 kg (IQR -12.5 to -2.9 kg, $p < 0.001$).

21 Relative Weight Change

22 Relative weight change is shown in Table 3. In general, these
23 reflected the patterns observed in absolute change. At 6 months
24 the largest weight increase was associated with a combination
25 therapy of metformin, sulphonylurea, insulin and TZD, with
26 an increase of 3.0% (IQR -0.4 to 6.9%, $p < 0.001$). The largest
27 reduction in weight was for metformin, insulin and exenatide,
28 with a reduction of -4.5% (IQR -8.1 to -0.7%, $p < 0.001$).

29 The largest weight increase at 12 months was for metformin,
30 sulphonylurea, insulin and TZD with an increase of 4.6%
31 (IQR -0.3 to 7.0%, $p < 0.001$). The largest weight decrease
32 at 12 months was associated with a combination therapy of
33 metformin and exenatide, with a decrease of -6.1% (IQR
34 -10.9 to -1.8%, $p < 0.001$).

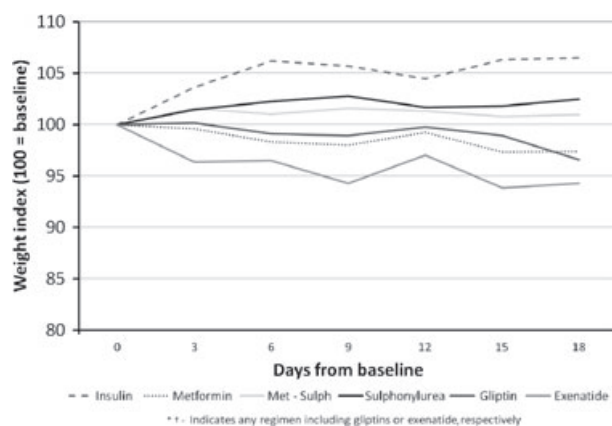
35 At 24 months the largest weight increase was for metformin,
36 sulphonylurea, insulin and TZD, with an increase of 6.25%
37 (IQR 2.4 to 10.75%, $p < 0.001$). The largest decrease was
38 for metformin and exenatide: -7.8% (IQR -11.4 to -2.2%,
39 $p < 0.001$).

41 Rolling Mean Weight by Treatment Regimen

42 Figure 2 shows the rolling weight average for insulin,
43 metformin and sulphonylurea monotherapies; metformin and
44 sulphonylurea combination therapy; and any combination
45 including DPP-4 inhibitors or exenatide. Both the insulin
46 and sulphonylurea monotherapies and the metformin plus
47 sulphonylurea therapy showed a consistent weight increase
48 from baseline. Metformin monotherapy was associated with an
49 initial gain followed by a decrease. Both the DPP-4 inhibitors
50 and exenatide showed a general downward trend.

52 Glucose Control—HbA1c

54 Over the corresponding period, mean HbA1c for patients
55 treated with insulin remained at 8.3%. For metformin, this fell
56 from 7.7 to 7.1%; for metformin and sulphonylurea combined,
57 it fell from 8.3 to 7.6%; and for sulphonylurea, it fell from
58 7.7 to 7.2%.



16 **Figure 2.** Sixty-day rolling average of weight for specific regimens from
17 baseline to 18 months.

18 Discussion

19 There was a continual increase in average weight for all patients
20 and for the subset of patients with T2DM between 1995 and
21 2010. For those without diabetes, there was an increase in mean
22 weight of 6.3 and 6.4 kg for males and females, respectively.
23 This was greater than the 5.1 and 3.4-kg observed in the
24 Health Survey for England for the same demographic group,
25 but inclusive of those with diabetes [16]. For T2DM, after
26 standardization for age, this increase was approximately 8.6 kg
27 for males and 6.3 kg for females. While we adjusted for age
28 and sex, it is possible that there may be other differences in
29 the cohorts at different time points. For example, the increased
30 emphasis on targeted screening for diabetes has led to the
31 identification of a less morbid population with T2DM [17]. As
32 body mass index is recommended as a filtering variable for
33 screening [18], it is likely that this will be reflected in the profile
34 of newly diagnosed cases. However, the pattern was consistent
35 over time rather than the sudden change that one would expect
36 if screening were influential.

37 The secular increase in weight may have significant clinical
38 consequences. To place the weight changes evident in this study
39 into context, the average reduction in weight at 2 years using
40 the antiobesity drug orlistat (120 mg) is around 6 kg (3.5 kg
41 vs. placebo) and slightly less at the lower dose [19]. If the
42 health benefits of weight loss claimed for such medications
43 are justifiable, common sense dictates that there must be
44 inverse consequences related to weight gain on diabetes-
45 related drugs. Weight gain in people with T2DM is associated
46 with reduced treatment adherence and health-related quality
47 of life [8,9]. Furthermore, weight gain may further heighten
48 the cardiovascular risk characteristic of T2DM [20]. A recent
49 population-based cohort study has, however, showed a normal
50 life expectancy in subjects with T2DM in primary care when
51 compared to the general population, which may reflect the
52 impact of multiple-risk-factor intervention in people with
53 T2DM [21].

54 As expected, alternative treatment regimens were associated
55 with differing patterns of weight change, with the greatest
56 increase in weight being associated with the complex
57 and unusual combination therapy of metformin, insulin,
58

1 sulphonylurea and TZD. Weight loss was most pronounced in
2 people treated with metformin plus exenatide, other metformin
3 combinations and regimens including exenatide and the DPP-
4 4 inhibitors. The analysis broadly confirmed clinical trial
5 experience, with regimens involving metformin, exenatide and
6 the DPP-4-inhibitors associated with weight loss, and insulin,
7 sulphonylurea and the TZDs associated with weight gain.

8 When treatments with different weight properties were used
9 in combination therapy, a modifying effect was observed. For
10 example, while at 24 months, insulin was associated with a
11 median increase of 4.5 kg and metformin with a decrease of
12 1.5 kg; in combination, there was an overall increase of only
13 2.4 kg. Consequently, when developing therapeutic strategies
14 for individual patients, the interaction of individual agents with
15 respect to weight should be considered.

16 There were study limitations. Weight was not collected
17 at precise times and we therefore lost patients who did not
18 have a valid weight measurement within prespecified time
19 frames. Patients who were frequently monitored for weight
20 were therefore more likely to be included in our cohort.

21 The progressive increase in weight observed in the T2DM
22 cohort may be partly accounted for by the increase in
23 obesity throughout society, in general [6,7]. However, the
24 introduction of evermore stringent glycaemic targets [1] and
25 the implementation of the Quality and Outcomes Framework in
26 the UK in 2004 [22] with its target-driven payment structure,
27 along with clinical trial data advocating intensive glycaemic
28 control [23], may have resulted in increased prescribing
29 of glucose-lowering therapies [22]. Such considerations may
30 contribute to the secular pattern of weight gain seen in
31 this analysis. Furthermore, hypoglycaemia, a recognized
32 consequence of intensified glycaemic control, particularly
33 with sulphonylurea and insulin therapy [24], often results in
34 defensive eating further contributing to weight gain. Indeed,
35 therapeutic approaches resulting in a low risk of hypoglycaemia,
36 such as metformin, DPP-4 inhibitors and exenatide [14], were
37 associated with modest secular downward trends in weight,
38 while the greatest reduction was noted with metformin plus
39 exenatide combination therapy, suggesting that the optimum
40 clinical utility of GLP-1 analogues may be obtained in
41 combination with metformin.

42 These observations and others [23] raise important ques-
43 tions relating to current therapeutic approaches to manag-
44 ing glycaemia. Treatment costs for T2DM in the UK have
45 almost doubled between 1997 and 2007 [23], largely driven
46 by increased prescription costs. During this period there has
47 been no improvement in overall glycaemic control [23]. The
48 relationship between weight gain and glycaemic control over
49 this period may represent both cause and effect, with increased
50 use of hypoglycaemic therapies contributing to weight gain and
51 weight gain representing a barrier to the improvement of gly-
52 caemic control. From the public health perspective, therefore,
53 it may be more pertinent to focus resources not on pharma-
54 cotherapy, but on the promotion of lifestyle modification to
55 reduce the incident risk of T2DM and to reduce weight in
56 people with established T2DM. Furthermore, intensification of
57 glycaemic control has not been shown to reduce all-cause mor-
58 tality in people with T2DM—and may even result in adverse

1 outcomes [25]—and this, coupled with the observations from
2 our analysis, supports the need to develop and implement an
3 individualized therapeutic approach.

4 Not only is the UK population in general continuously
5 increasing in weight—thus adding to the burden of
6 T2DM—but also those with T2DM are continuously
7 increasing in weight. At a population level, there is depressingly
8 little evidence that any treatment regimen is impacting upon
9 what is conventionally the primary purpose of diabetes-related
10 treatment, that is, glucose control.

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34 Conflict of Interest

35 C. Ll. M researched data, contributed to discussion, and wrote
36 and reviewed the manuscript; S. J-J. researched data and edited
37 the manuscript; M. E, A. H. B. and C. D. P. contributed to
38 discussion and reviewed the manuscript; C. J. C contributed to
39 discussion and wrote and reviewed the manuscript.

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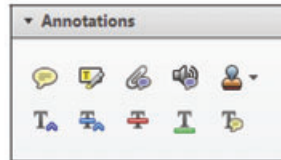
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Once you have Acrobat Reader open on your computer, click on the **Comment** tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the **Annotations** section, pictured opposite. We've picked out some of these tools below:



1. Replace (Ins) Tool – for replacing text.

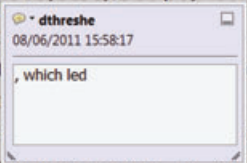


Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the **Replace (Ins)** icon in the Annotations section.
- Type the replacement text into the blue box that appears.

standard framework for the analysis of microeconomics. Nevertheless, it also led to the development of a number of strategic substitutes. The number of competitors in the industry is that the structure of the industry is an important determinant of the level, are exogenous variables. The important work on entry by Dixit and Stiglitz (henceforth) we open the 'black b



2. Strikethrough (Del) Tool – for deleting text.



Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the **Strikethrough (Del)** icon in the Annotations section.

there is no room for extra profits and mark-ups are zero and the number of firms (net) values are not determined by Blanchard and Kiyotaki (1987), perfect competition in general equilibrium of aggregate demand and supply in a classical framework assuming monopoly. An exogenous number of firms

3. Add note to text Tool – for highlighting a section to be changed to bold or italic.



Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the **Add note to text** icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

dynamic responses of mark-ups are consistent with the VAR evidence

sation of the number of firms in the industry. The number of competitors and the markup is that the structure of the sector is also with the demand



4. Add sticky note Tool – for making notes at specific points in the text.

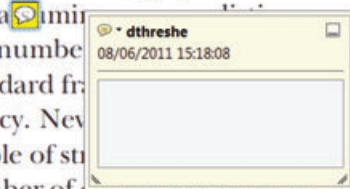


Marks a point in the proof where a comment needs to be highlighted.

How to use it


- Click on the **Add sticky note** icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.

and supply shocks. Most of the variation in the number of firms in the industry is that the structure of the sector is also with the demand



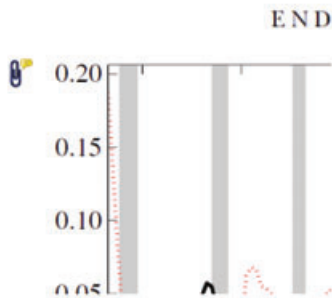
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.


 Inserts an icon linking to the attached file in the appropriate place in the text.

How to use it

- Click on the **Attach File** icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.



6. Add stamp Tool – for approving a proof if no corrections are required.

 Inserts a selected stamp onto an appropriate place in the proof.

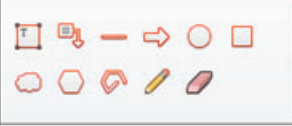
How to use it

- Click on the **Add stamp** icon in the Annotations section.
- Select the stamp you want to use. (The **Approved** stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).

...of the business cycle, starting with the
 ...on perfect competition, constant ret
 ...production. In this environment, goods
 ...extraordinary returns to scale are
 ...he... determined by the model. The New-Key
 ...otaki (1987), has introduced produc
 ...general equilibrium models with nomin



Drawing Markups

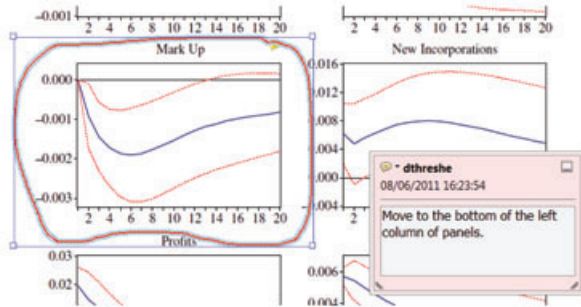


7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

How to use it

- Click on one of the shapes in the **Drawing Markups** section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



For further information on how to annotate proofs, click on the **Help** menu to reveal a list of further options:

