



Deposited via The University of Leeds.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/112636/>

Version: Accepted Version

Article:

Schlesinger, S, Aleksandrova, K, Abar, L et al. (2017) Adult weight gain and colorectal adenomas – a systematic review and meta-analysis. *Annals of Oncology*, 28 (6). pp. 1217-1229. ISSN: 0923-7534

<https://doi.org/10.1093/annonc/mdx080>

(c) The Author 2017. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. This is a pre-copyedited, author-produced PDF of an article accepted for publication in the *Annals of Oncology* following peer review. The version of record, 'Schlesinger, S, Aleksandrova, K, Abar, L et al (2017) Adult weight gain and colorectal adenomas – a systematic review and meta-analysis. *Annals of Oncology*. mdx080,' is available online at: <https://doi.org/10.1093/annonc/mdx080>

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

1
2
3
4 **Article type:** Review
5
6
7

8 **Title:** Adult weight gain and colorectal adenomas – a systematic review and meta-analysis
9
10

11 **Authors:** S. Schlesinger^{1,2}, K. Aleksandrova³, L. Abar¹, A.R. Viera¹, S. Vingeliene¹, E.
12 Polemiti¹, C.A.T.Stevens¹, D.C. Greenwood⁴, D.S.M. Chan¹, D. Aune^{1,5}, T. Norat¹
13
14
15
16
17
18

19 **Affiliations:** ¹ Department of Epidemiology and Biostatistics, School of Public Health, Imperial
20 College London, UK; ² Junior Research Group Systematic Reviews, Institute for Biometrics and
21 Epidemiology, German Diabetes Center, Düsseldorf, Germany; ³ Nutrition, Immunity and
22 Metabolism Start-up Lab, Department of Epidemiology, German Institute of Human Nutrition
23 Potsdam-Rehbrücke, Nuthetal, Germany; ⁴ Division of Epidemiology and Biostatistics, School
24 of Medicine, University of Leeds, Leeds, UK, ⁵ Bjørknes University College, Oslo, Norway
25
26
27
28
29
30
31
32
33
34
35

36 **Corresponding author:** Dr. Sabrina Schlesinger, Imperial College London, School of Public
37 Health, Department of Epidemiology and Biostatistics, St. Mary's Campus, Norfolk Place,
38 Paddington, London W2 1PG, UK, Tel: 0044 20 7594 8478, s.schlesinger@imperial.ac.uk
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Abstract.**
4

5 **Background:** Colorectal adenomas are known as precursors for the majority of colorectal
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138
2139
2140
2141
2142
2143
2144
2145
2146
2147
2148
2149
2150
2151
2152
2153
2154
2155
2156
2157
2158
2159
2160
2161
2162
2163
2164
2165
2166
2167
2168
2169
2170
2171
2172
2173
2174
2175
2176
2177
2178
2179
2180
2181
2182
2183
2184
2185
2186
2187
2188
2189
2190
2191
2192
2193
2194
2195
2196
2197
2198
2199
2200
2201
2202
2203
2204
2205
2206
2207
2208
2209
2210
2211
2212
2213
2214
2215
2216
2217
2218
2219
2220
2221
2222
2223
2224
2225
2226
2227
2228

1
2
3 1 **Key words:** Body weight gain, body weight change, colorectal adenomas, polyps, meta-analysis,
4
5 2 observational studies
6
7
8 3
9
10 4
11

12 5 **Key message:** This is the first systematic review and meta-analysis summarizing evidence on
13 6 adult body weight gain and colorectal adenomas. Per 5 kg body weight gain the odds of adenoma
14 7 occurrence increased by 7% (2%-11%). These findings show the benefits of weight control from
15 8 early adulthood regarding the occurrence of colorectal adenomas, which might be relevant for
16 9 early colorectal cancer prevention.
17
18
19
20
21
22
23
24 10
25
26
27 11
28
29 12
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Introduction.

2 In 2012, colorectal cancer was the third most common cancer in men and the second in
3 women, and about 694,000 deaths from colorectal cancer were documented worldwide.[1] Many
4 modifiable lifestyle factors, including smoking, dietary factors, physical activity as well as
5 obesity and weight gain during adulthood have been identified as influencing factors for risk of
6 colorectal cancer.[2, 3] There is consent that adenomas –non-cancerous tumors– in the colon or
7 rectum are precursors to development of colorectal cancer, known as the adenoma-to-carcinoma
8 sequence.[4, 5] Regarding this aspect, it is likely that the same risk factors as for colorectal
9 cancer are involved in the etiology of colorectal adenomas. A growing body of evidence suggest
10 that smoking,[6] physical activity,[7] dietary intake of fiber,[8] meat,[9] and alcohol,[10] are also
11 associated with risk of colorectal adenomas, and serrated adenomas,[11] a subtype with strong
12 malignant potential.[12] In addition, body fatness –both general and abdominal– has been linked
13 to increased risk of colorectal adenomas.[13-16] A recent meta-analysis indicated that the
14 visceral adipose tissue, related to metabolic adverse effects is associated with advanced
15 colorectal adenomas and might be a mediator for the association between obesity and colorectal
16 adenomas.[17] Moreover, adult weight gain, a marker of body fat mass fluctuation, is related to
17 metabolic alterations as well, even within the normal body weight range and already during early
18 adulthood.[18] [19] In this context, beyond body fatness, epidemiological studies have
19 investigated whether adult weight gain is related to the occurrence and recurrence of colorectal
20 adenomas. Even though most studies indicated a positive association between adult weight gain
21 and risk of colorectal adenomas, some of these findings still allowed for the possibility of no
22 increase in risk and uncertainty remains in the exact magnitude of any association.[20-29]. So

1 far, no systematic review or meta-analysis has been conducted that summarize findings on this
2 association.

3 Thus, to quantify this association we conducted a meta-analysis of epidemiological
4 studies (including cross-sectional, case-control and prospective studies) on adult weight gain and
5 colorectal adenomas and recurrence. In addition, we explored linear and non-linear dose-
6 response relations on adult weight change and the occurrence of colorectal adenomas. And
7 finally, we investigated if study design, sex, adenoma location (colon vs. rectum), time period of
8 weight assessment (weight gain in early adulthood vs during middle age), and adjustment for
9 general body fatness might influence the association between adult weight gain and colorectal
10 adenoma occurrence.

11 12 **Materials and Methods.**

13 This report was conducted according to standard criteria provided by the Meta-analysis Of
14 Observational Studies in Epidemiology (MOOSE) group.[30]

15 *Literature Search*

16 The literature search has been conducted as part of the World Cancer Research Fund
17 International Continuous Update Project/ American Institute for Cancer Research Continuous
18 Update Project following a predefined protocol
19 (http://www.wcrf.org/sites/default/files/protocol_colorectal_cancer.pdf). Relevant studies on
20 weight gain during adulthood and colorectal adenomas were identified by searching PubMed up
21 to December 2015. Initially (up to December 2005), several other databases were used, including
22 Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane library, CINAHL,
23 AMED, National Research Register and In Process Medline. As all the relevant studies were

1 identified using PubMed, a change in the protocol was made and only PubMed was used for the
2 updated searches. The literature search included two outcomes, colorectal cancer and colorectal
3 adenomas. As this systematic review and meta-analysis focus on colorectal adenomas only, we
4 excluded studies on colorectal cancer. We conducted an update of the literature search in
5 Medline (PubMed) for articles on adult weight change and colorectal adenomas until September
6 2016.

8 *Study selection*

9 Studies were selected if they 1) reported on the association between adult weight change
10 and adenoma occurrence or recurrence, 2) used a cohort, nested case-control, case-cohort, case-
11 control, cross-sectional design, or follow-up studies of randomized clinical trials, and 3)
12 provided effect estimates for this association (including hazard ratio or odds ratio (OR)) with the
13 95% confidence interval (95% CIs). For simplicity, we use the term OR for all these estimates in
14 the present manuscript. In addition, we defined studies as prospective if a follow-up period
15 between second weight assessment and diagnosis of colorectal adenomas was available and as
16 retrospective if the second weight measure was taken at time of colorectal adenoma assessment
17 or recalled 1 year before. We focused on two different outcomes: adenoma occurrence (no
18 previous adenoma was known) and adenoma recurrence (prior adenoma was diagnosed). Studies
19 not published as original articles were excluded. Furthermore, we excluded one study reporting
20 on changes of BMI instead of weight change because a conversion into weight change was not
21 possible.[31]

23 *Data extraction*

1 The following information was extracted from each study: last name of the first author,
2 publication year, country of origin, underlying study source, duration of follow-up (if
3 applicable), sex, age (range or mean), outcome (occurrence or recurrence), outcome assessment,
4 sample size, number of cases, number of controls (if applicable), assessment of weight change
5 and age at weight assessment, quantity of weight change, most fully adjusted estimates and
6 corresponding 95% CIs, and variables adjusted for in the statistical analysis. Data for men and
7 women, or colon and rectal adenomas, were extracted separately, if information was provided by
8 the single studies.

9 10 *Statistical analysis*

11 The associations between weight gain during adulthood and colorectal adenoma
12 occurrence or recurrence were analyzed by comparing extreme categories of weight gain during
13 adulthood (high weight gain vs. low weight gain), and summary ORs (95% CI) were calculated
14 by applying random effects models. Two studies reported on adult weight gain in pounds,[24,
15 26] and quantifications were converted in kg (1 kg \cong 2.2 lbs). For one study, we converted adult
16 weight change in kg/year into weight change per kg by multiplying the quantification with the
17 time interval between both weight assessments.[28] If stable weight was not used as reference
18 category in single studies,[21, 23] we used the method of Hamling *et al.* to convert risk estimates
19 to being relative to this reference category.[32] For studies that reported estimates stratified by
20 sex,[22] or adenoma site (colon, rectal and both),[29] a fixed effect model was used to combine
21 the estimates for the main analysis.

22 Heterogeneity between studies was investigated by using the I^2 test and to investigate
23 potential influencing factors for the association between adult weight gain and colorectal

1 adenoma occurrence, we performed subgroup and meta-regression analyses.[33] We stratified
2 our analysis by: study design (prospective vs. retrospective), sex (men vs. women), site of
3 adenoma (colon vs. rectum), time of weight assessment (early vs. mid-life adulthood), definition
4 of high weight gain category (≥ 10 vs < 10 kg), used reference category (weight loss included vs.
5 stable weight), outcome assessment (colonoscopy vs. sigmoidoscopy vs. self-reports), geographic
6 area (Asia vs. Europe vs. USA), indication (without indication vs. with indication), and
7 adjustment (yes vs. no) for baseline weight/body mass index/waist circumference, physical
8 activity, smoking, alcohol intake, and family history of colorectal cancer. Stratified analyses for
9 adenoma recurrence were not conducted because of the restricted number of studies.

10 Furthermore, we performed a linear dose-response meta-analysis of the association
11 between adult weight gain per 5 kg and colorectal adenoma occurrence. Study-specific slopes
12 (linear trends) and 95% CIs from the natural logarithm of the ORs across categories of weight
13 change were calculated by using the method described by Greenland and Longnecker and
14 implemented by Orsini.[34, 35] This method requires the distribution of cases, person-years/non-
15 cases, the quantification of the exposure and the risk estimates with corresponding 95% CIs for
16 at least three weight change categories. The distribution of cases, person years or non-cases was
17 estimated if the information was missing. The mid-point between the lower and upper limit for
18 each exposure category was calculated, if studies reported ranges and mean values were not
19 reported. When the lowest or highest category was open-ended, we expected that the range was
20 similar to the adjacent category. Some of the studies included weight loss in the reference
21 category, and we excluded these studies in a sensitivity analysis.[20, 25, 27] In another
22 sensitivity analysis, we repeated the dose-response meta-analysis stratified by study design. In

1 addition, we investigated adult weight gain per kg/year to consider different time periods
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 addition, we investigated adult weight gain per kg/year to consider different time periods
2 between the both weight assessments.

3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

3 Moreover, a potential non-linear relation between weight change during adulthood and
4 colorectal adenoma occurrence was investigated by performing cubic spline regression models
5 and indication of non-linearity was tested by using likelihood ratio test.[36] We included all
6 categories of weight change (even the weight loss categories) to get an idea about the whole
7 relation between weight change and occurrence of colorectal adenoma. We repeated the non-
8 linear dose-response meta-analysis only including prospective studies. For adenoma recurrence
9 the number of studies was restricted and we were not able to investigate the dose-response
10 relation.

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

11 Small study effects such as publication bias were assessed by visual inspection of the
12 funnel plot for asymmetry and by applying Egger's test.[37]

13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

13 All statistical analyses were performed using STATA version 13.1 software (StataCorp,
14 College Station, TX).

15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

16 **Results.**

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

17 The flow chart of the literature search is shown in **Figure 1**. In total, we included 10
18 studies (6 retrospective and 4 prospective studies)[20-29] on adult weight change and colorectal
19 adenomas in our meta-analysis, with 9 studies focusing on occurrence[20-23, 25-29] and 3
20 studies on recurrence.[22-24] The characteristics of included studies are shown in **Table 1**.

21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

22 *Adenoma Occurrence*

1 The association between weight gain during adulthood and colorectal adenoma
2 occurrence was investigated in 9 studies (5 retrospective and 4 prospective studies), [20-23, 25-
3 29] including 5,507 cases among 59,187 participants. Out of these, weight gain was assessed
4 during early adulthood in 6 and during mid-life in 3 studies.

5 In the meta-analysis comparing high (midpoint 17.4 kg) versus low weight gain during
6 adulthood, the summary OR for colorectal adenoma occurrence was 1.39 (95% CI: 1.17-1.65)
7 with moderate heterogeneity (I^2 : 43%, $P_{heterogeneity}=0.08$) (**Figure 2**).

8 Subgroup analyses are shown in **Table 2**. The findings stratified by sex suggested that the
9 association was stronger in women [summary OR (95% CI) 1.36 (1.01-1.83); $N=4$ studies]
10 compared to men [summary OR (95% CI) 1.05 (0.71-1.55); $N=3$ studies], but differences were
11 not statistically significant (P for heterogeneity by sex=0.51). When we restricted the stratified
12 analysis by sex to studies providing both information (for men and women separately, $N=2$
13 studies), the summary OR for women was 0.78 (95% CI: 0.31-1.95) and for men 1.15 (95% CI:
14 0.46-2.86), with no indication for interaction (P for heterogeneity by sex=0.68). Stronger
15 associations were observed for studies which defined high adult weight gain as greater or equal
16 than 10 kg [summary OR (95% CI) 1.55 (1.26-1.90)] compared to studies investigating less than
17 10 kg [summary OR (95% CI) 1.24 (0.95-1.63)]; but differences were not statically significant
18 (P for heterogeneity by weight gain category=0.21). We did not observe a difference of the
19 association after stratification by study design (prospective vs. retrospective studies) (**Table 2**
20 and **Supplementary figure S1**) and adjustment for excess body weight (**Table 2**).

21 In other subgroup analyses (stratification by site of adenoma, time of weight assessment,
22 geographic area, indication and study quality criteria, such as definition of reference category,

1 outcome assessment, adjustment for confounders) the findings remained robust and no
2 statistically significant differences were observed.

3 For the dose-response meta-analysis we included 7 studies.[20, 21, 23, 25, 27-29] Per
4 each 5 kg weight gain during adulthood the odds of colorectal adenoma was increased by 7%
5 (95% CI: 2%-11%) (**Figure 3**). There was moderate to high heterogeneity (I^2 : 65%,
6 $P_{heterogeneity}=0.009$), In a sensitivity analysis, excluding studies using a combination of adult
7 weight gain and weight loss in the reference category,[23, 28, 29, 38] the odds of colorectal
8 adenoma was slightly higher [summary OR (95% CI) per 5 kg weight gain during adulthood:
9 1.08 (1.03-1.12), $N=4$ studies)] and there was no indication for heterogeneity between the
10 studies (I^2 : 0%, $P_{heterogeneity}=0.87$). No differences by study design (prospective vs retrospective)
11 was observed (**Supplementary figure S2**). The non-linear dose-response curve indicated
12 evidence of non-linearity ($P_{non-linearity}<0.001$), but no threshold of adult weight gain in relation to
13 risk increase was observed. The curve shows an increase odds of colorectal adenoma throughout
14 all the range of adult weight gain investigated, although the curve was steeper at lower levels of
15 weight gain than at higher levels (**Figure 4**). After restricting our non-linear dose-response meta-
16 analysis to prospective studies only, findings did not change substantially (**Supplementary**
17 **figure S3**). When we considered the time interval of weight gain during adulthood, the odds of
18 colorectal adenoma was 30 % increased by each kg adult weight gain per year [summary OR
19 (95% CI) for 1 kg/y: 1.30 (1.10-1.55); I^2 : 70%, $P_{heterogeneity}=0.003$].

20 There was no indication for publication bias (Egger's test: $P=0.57$; **Supplementary**
21 **figure S4**)

22
23 *Adenoma Recurrence*

1 For the analysis on weight gain during adulthood and adenoma recurrence we included 3
2 studies (2 retrospective and 1 prospective studies),[22-24] including 1,350 cases among 5,559
3 participants. One study reported on weight gain during early adulthood and 2 on weight gain
4 during mid-life. The summary OR (95% CI) in high versus low meta-analysis was 1.14 (0.88-
5 1.49), without statistically significant indication of heterogeneity between studies ($I^2=48\%$,
6 $P_{heterogeneity}=0.15$) (**Figure 2**). We did not conduct subgroup analyses, linear and non-linear dose-
7 response meta-analysis of weight gain and adenoma recurrence because of the limited number of
8 studies.

10 **Discussion.**

11 This is the first systematic review and meta-analysis reporting on the association between
12 weight gain during adulthood and colorectal adenomas. Findings indicated that high adult weight
13 gain was associated with higher odds of adenoma occurrence. For a 5 kg weight gain during
14 adulthood the odds of colorectal adenoma occurrence increased by 7%. Although there was
15 indication for a non-linear relation, with a slightly steeper relation at lower than higher values of
16 weight gain, the curve shows an increased odds of colorectal adenomas throughout all the range
17 of adult weight gain investigated and a reduction in odds of adenoma occurrence with weight
18 loss. For adenoma recurrence the number of studies was too limited to draw clear conclusions.

19 Our findings on adult weight gain during adulthood and colorectal adenoma occurrence
20 are comparable with findings on weight gain and risk of colorectal cancer.[3] Our findings
21 indicated that for each 5 kg gain in weight during adulthood the odds of colorectal adenoma
22 increased by 7% (2%-11%), and the risk for colorectal cancer by 4% (2%-5%).[3] In addition,
23 these findings are in line with previous reports on anthropometric measures, including measures

1 of general and abdominal obesity as well as quantification of specific fat depots, showing
2 positive associations between body fatness and colorectal adenomas.[13-17, 39]

3 We did not identify statistically significant differences in subgroups analyses, but
4 findings need more consideration. After stratification by sex, findings indicated that the
5 association was restricted to women and not significant in men, however, the low number of
6 studies in these subgroup analyses is a limitation. To explore if these findings might be
7 influenced by other characteristics of the studies, we restricted this analysis only to studies that
8 provided findings for both, men and women separately.[22, 23] These two studies, one
9 conducted in Korea, including participants undergoing a screening program, and the other study
10 from the Netherlands, including participants with MMR gene mutation carrier, indicated that
11 associations were stronger in men than in women, but differences were not statistically
12 significant.[22, 23] The meta-analysis on weight gain during adulthood and risk of colorectal
13 cancer provided evidence that the association was stronger in men than in women,[3] whereas
14 findings on anthropometric measures and colorectal adenoma did not show differences between
15 men and women.[13, 15-17] However, for colorectal adenoma the number of studies accounting
16 for men and women separately is limited and studies focusing on differences are warranted.
17 After stratification by site, we did not observe statistically significant differences between colon
18 and rectal adenomas with weight gain during adulthood, which is comparable to previous
19 findings on colorectal cancer.[3] But again, number of studies were limited and further studies
20 are needed. We stratified our analysis by studies adjusting and not adjusting for body fatness
21 defined by weight, BMI, or waist circumference. The results did not differ appreciably between
22 the two groups, indicating that weight gain during adulthood is associated with colorectal
23 adenoma, independently of body fatness.

1 The underlying mechanism for the association between adult weight change and adenoma
2 occurrence is not clear yet. Lifestyle intervention studies provided evidence that weight loss
3 improved levels of oxidative stress (including CRP, oxidized low-density lipoprotein, fluorescent
4 oxidation products, F2-isoprostanes), metabolic biomarkers (including leptin and adiponectin)
5 and insulin resistance,[40-43] whereas observational studies indicated that body weight gain
6 during adulthood is related with metabolic alterations.[18, 19, 44] Recently, a large European
7 cohort study reported that individuals with normal weight but a metabolic unhealthy status
8 (defined by hyperinsulinaemia) were at higher risk of colorectal cancer compared to metabolic
9 healthy and normal weight individuals.[45] This study also showed that overweight individuals,
10 but metabolically healthy were at lower risk of colorectal cancer compared to overweight
11 individuals who were metabolic unhealthy. These findings underline the hypothesis that
12 metabolic alterations beyond BMI might play a role in the etiology of colorectal cancer. While
13 metabolic perturbations are associated with increased risk of colorectal cancer,[38, 45-48] the
14 evidence for colorectal adenomas is less clear,[49-52] explainable by the lack of studies,
15 particularly prospective studies.[53] Findings from case-control and cross-sectional studies
16 indicated that the prevalence of the metabolic syndrome and insulin resistance was higher and
17 levels of adiponectin lower in individuals with colorectal adenoma compared to the control
18 group,[52, 54, 55] which might be a potential explanation for our observed association. More
19 studies investigating the pathomechanisms of colorectal adenomas in relation with adult weight
20 gain and body fatness in general, are needed.

21 Our meta-analysis has several strengths. First, to our knowledge this is the first
22 systematic review and meta-analysis summarizing the evidence between body weight gain
23 during adulthood and colorectal adenoma. Second, this report does not focus on high versus low

1
2
3 1 analysis only, but linear and non-linear dose-response analysis were conducted to explore the
4
5
6 2 strength and shape of the relation between adult weight gain and colorectal adenoma occurrence.
7
8 3 Third, we performed stratified analysis to investigate the robustness of our findings, considering
9
10 4 biological and methodological factors. In this context, we could show that the association
11
12 5 persisted even after adjusting for body fatness, defined by weight, BMI, or waist circumference.
13
14 6 On the contrary, our study has limitations that should be discussed. First our study included both,
15
16 7 retrospective and prospective studies. However, we stratified our meta-analysis by study design
17
18 8 and findings were comparable. In addition, most of the studies included asymptomatic
19
20 9 individuals and only two studies were based on individuals with indications. In our stratified
21
22 10 analyses results did not change considerably, making recall bias from case-control or cross-
23
24 11 sectional studies less likely. Second, some of the studies included in our meta-analysis relied on
25
26 12 colorectal adenoma detection rather than onset and it is possible that adenomas have developed
27
28 13 earlier. If studies did not conduct a colonoscopy at baseline for cohort studies or in the past for
29
30 14 case-control and cross-sectional studies, prevalent colorectal adenomas are likely included,
31
32 15 which might have an influence on the temporal sequence of the relation between adult weight
33
34 16 change and colorectal adenoma occurrence. However, as discussed earlier colorectal adenomas
35
36 17 mostly do not show any symptoms and it is unlikely that participants changed their weight
37
38 18 intentionally. In addition, a previous meta-analysis showed that unintentional weight loss was
39
40 19 less than 10% for individuals diagnosed with colorectal adenomas.[56] Third, measurement error
41
42 20 of adult weight gain cannot be ruled out. For early weight gain information was based on
43
44 21 recalled weight, which might be a valid measurement,[57, 58] but tended to be underreported
45
46 22 depending on the current weight and amount of weight gain.[59] If body weight was
47
48 23 underestimated in the studies included in our meta-analysis, estimates would be biased toward

1
2
3 1 the null. Fourth, the analysis on adenoma recurrence and subgroup analyses by sex and adenoma
4
5 2 site were restricted by the small number of studies providing the information separately. These
6
7
8 3 findings should be interpreted with caution and more studies investigating sex- and site-specific
9
10 4 associations between adult weight gain and colorectal adenoma occurrence and recurrence are
11
12 5 warranted.

13
14
15 6 In conclusion, this meta-analysis indicated evidence that weight change during adulthood
16
17 7 is associated with colorectal adenoma occurrence independently of excess body weight. In the
18
19 8 non-linear dose-response meta-analysis, colorectal adenomas were less common in individuals
20
21 9 reporting weight loss and more common in individuals with weight gain. Even a small amount of
22
23 10 adult weight gain was related to higher odds of colorectal adenoma. Our findings show the
24
25 11 benefits of weight control from early adulthood regarding the occurrence of colorectal adenomas
26
27
28 12 – a known precursor of colorectal cancer – which might be relevant for early prevention.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Funding:** The work of DSMC, LA, ARV, SV, EP, CATS and TN was supported by the World
2 Cancer Research Fund International as part of the Continuous Update Project (grant number:
3 2007/SP01). The work of SS and DA was supported by a NHS BRC grant (Interventional Public
4 Health). The views expressed in this review are the opinions of the authors. The views may not
5 represent the views of World Cancer Research Fund International/ American Institute for Cancer
6 Research and may differ from those in future updates of the evidence related to food, nutrition,
7 physical activity, and cancer risk. The sponsor of this study had no role in the decisions about the
8 analysis or interpretation of the data; or preparation, review, or approval of the manuscript.

9

10 **Disclosures:** The authors have declared no conflicts of interest.

11

12

1 **References**

- 2 1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide:
3 sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136: E359-386.
- 4 2. World Cancer Research Fund / American Institute for Cancer Research.
5 Continuous Update Project Report. Food N, Physical Activity, and the Prevention of Colorectal
6 Cancer. 2011.
- 7 3. Schlesinger S, Lieb W, Koch M et al. Body weight gain and risk of colorectal cancer: a
8 systematic review and meta-analysis of observational studies. *Obes Rev* 2015; 16: 607-619.
- 9 4. Strum WB. Colorectal Adenomas. *N Engl J Med* 2016; 374: 1065-1075.
- 10 5. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; 61:
11 759-767.
- 12 6. Botteri E, Iodice S, Raimondi S et al. Cigarette smoking and adenomatous polyps: a
13 meta-analysis. *Gastroenterology* 2008; 134: 388-395.
- 14 7. Wolin KY, Yan Y, Colditz GA. Physical activity and risk of colon adenoma: a meta-
15 analysis. *Br J Cancer* 2011; 104: 882-885.
- 16 8. Ben Q, Sun Y, Chai R et al. Dietary fiber intake reduces risk for colorectal adenoma: a
17 meta-analysis. *Gastroenterology* 2014; 146: 689-699 e686.
- 18 9. Aune D, Chan DS, Vieira AR et al. Red and processed meat intake and risk of colorectal
19 adenomas: a systematic review and meta-analysis of epidemiological studies. *Cancer Causes*
20 *Control* 2013; 24: 611-627.
- 21 10. Ben Q, Wang L, Liu J et al. Alcohol drinking and the risk of colorectal adenoma: a dose-
22 response meta-analysis. *Eur J Cancer Prev* 2015; 24: 286-295.

- 1
2
3 11. Bailie L, Loughrey MB, Coleman HG. Lifestyle Risk Factors for Serrated Colorectal
4 Polyps: a Systematic Review and Meta-analysis. *Gastroenterology* 2016.
5
6
7
8 12. Gao Q, Tsoi KK, Hirai HW et al. Serrated polyps and the risk of synchronous colorectal
9 advanced neoplasia: a systematic review and meta-analysis. *Am J Gastroenterol* 2015; 110: 501-
10 509.
11
12
13
14 13. Ben Q, An W, Jiang Y et al. Body mass index increases risk for colorectal adenomas
15 based on meta-analysis. *Gastroenterology* 2012; 142: 762-772.
16
17
18 14. Hong S, Cai Q, Chen D et al. Abdominal obesity and the risk of colorectal adenoma: a
19 meta-analysis of observational studies. *Eur J Cancer Prev* 2012; 21: 523-531.
20
21
22
23 15. Lee YJ, Myung SK, Cho B et al. Adiposity and the risk of colorectal adenomatous
24 polyps: a meta-analysis. *Cancer Causes Control* 2011; 22: 1021-1035.
25
26
27
28 16. Okabayashi K, Ashrafian H, Hasegawa H et al. Body mass index category as a risk factor
29 for colorectal adenomas: a systematic review and meta-analysis. *Am J Gastroenterol* 2012; 107:
30 1175-1185.
31
32
33
34 17. Keum N, Lee DH, Kim R et al. Visceral adiposity and colorectal adenomas: dose-
35 response meta-analysis of observational studies. *Ann Oncol* 2015; 26: 1101-1109.
36
37
38 18. Alley DE, Chang VW. Metabolic syndrome and weight gain in adulthood. *J Gerontol A*
39 *Biol Sci Med Sci* 2010; 65: 111-117.
40
41
42
43 19. Bot M, Spijkerman AM, Twisk JW, Verschuren WM. Weight change over five-year
44 periods and number of components of the metabolic syndrome in a Dutch cohort. *Eur J*
45 *Epidemiol* 2010; 25: 125-133.
46
47
48
49 20. Bird CL, Frankl HD, Lee ER, Haile RW. Obesity, weight gain, large weight changes, and
50 adenomatous polyps of the left colon and rectum. *Am J Epidemiol* 1998; 147: 670-680.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 21. Kono S, Handa K, Hayabuchi H et al. Obesity, weight gain and risk of colon adenomas in
4
5
6 2 Japanese men. *Jpn J Cancer Res* 1999; 90: 805-811.
7
8 3 22. Botma A, Nagengast FM, Braem MG et al. Body mass index increases risk of colorectal
9
10 4 adenomas in men with Lynch syndrome: the GEOLynch cohort study. *J Clin Oncol* 2010; 28:
11
12 5 4346-4353.
13
14
15 6 23. Jung YS, Park JH, Park DI et al. Weight Change and Obesity Are Associated with a Risk
16
17 7 of Adenoma Recurrence. *Dig Dis Sci* 2016; 61: 2694-2703.
18
19
20 8 24. Laiyemo AO, Doubeni C, Badurdeen DS et al. Obesity, weight change, and risk of
21
22 9 adenoma recurrence: a prospective trial. *Endoscopy* 2012; 44: 813-818.
23
24
25 10 25. Lubin F, Rozen P, Arieli B et al. Nutritional and lifestyle habits and water-fiber
26
27 11 interaction in colorectal adenoma etiology. *Cancer Epidemiol Biomarkers Prev* 1997; 6: 79-85.
28
29
30 12 26. Sedjo RL, Byers T, Levin TR et al. Change in body size and the risk of colorectal
31
32 13 adenomas. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 526-531.
33
34
35 14 27. Wise LA, Rosenberg L, Palmer JR, Adams-Campbell LL. Anthropometric risk factors for
36
37 15 colorectal polyps in African-American women. *Obesity (Silver Spring)* 2008; 16: 859-868.
38
39 16 28. Morois S, Mesrine S, Josset M et al. Anthropometric factors in adulthood and risk of
40
41 17 colorectal adenomas: The French E3N-EPIC prospective cohort. *Am J Epidemiol* 2010; 172:
42
43 18 1166-1180.
44
45
46 19 29. Wernli KJ, Newcomb PA, Wang Y et al. Body size, IGF and growth hormone
47
48 20 polymorphisms, and colorectal adenomas and hyperplastic polyps. *Growth Horm IGF Res* 2010;
49
50 21 20: 305-309.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 30. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in
4
5
6 2 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology
7
8 3 (MOOSE) group. JAMA 2000; 283: 2008-2012.
9
10 4 31. Siddiqui A, Chang M, Mahgoub A, Sahdala HN. Increase in body size is associated with
11
12 5 an increased incidence of advanced adenomatous colon polyps in male veteran patients.
13
14 6 Digestion 2011; 83: 288-290.
15
16
17 7 32. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving
18
19 8 relative effect and precision estimates for alternative comparisons from a set of estimates
20
21 9 presented by exposure level or disease category. Stat Med 2008; 27: 954-970.
22
23
24 10 33. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;
25
26 11 21: 1539-1558.
27
28
29 12 34. Orsini N, Li R, Wolk A et al. Meta-analysis for linear and nonlinear dose-response
30
31 13 relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012; 175:
32
33 14 66-73.
34
35
36 15 35. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-
37
38 16 response data, with applications to meta-analysis. Am J Epidemiol 1992; 135: 1301-1309.
39
40
41 17 36. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989; 8:
42
43 18 551-561.
44
45
46 19 37. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a
47
48 20 simple, graphical test. BMJ 1997; 315: 629-634.
49
50
51 21 38. Jenab M, Riboli E, Cleveland RJ et al. Serum C-peptide, IGFBP-1 and IGFBP-2 and risk
52
53 22 of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition.
54
55 23 Int J Cancer 2007; 121: 368-376.
56
57
58
59
60

- 1
2
3 1 39. Omata F, Deshpande GA, Ohde S et al. The association between obesity and colorectal
4
5
6 2 adenoma: systematic review and meta-analysis. *Scand J Gastroenterol* 2013; 48: 136-146.
7
8 3 40. Duggan C, Tapsoba JD, Wang CY et al. Dietary Weight Loss, Exercise, and Oxidative
9
10 4 Stress in Postmenopausal Women: A Randomized Controlled Trial. *Cancer Prev Res (Phila)*
11
12 5 2016; 9: 835-843.
13
14 6 41. Abbenhardt C, McTiernan A, Alfano CM et al. Effects of individual and combined
15
16 7 dietary weight loss and exercise interventions in postmenopausal women on adiponectin and
17
18 8 leptin levels. *J Intern Med* 2013; 274: 163-175.
19
20 9 42. Rock CL, Flatt SW, Pakiz B et al. Effects of diet composition on weight loss, metabolic
21
22 10 factors and biomarkers in a 1-year weight loss intervention in obese women examined by
23
24 11 baseline insulin resistance status. *Metabolism* 2016; 65: 1605-1613.
25
26 12 43. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a
27
28 13 systematic review. *Arch Intern Med* 2007; 167: 31-39.
29
30 14 44. Montonen J, Boeing H, Schleicher E et al. Association of changes in body mass index
31
32 15 during earlier adulthood and later adulthood with circulating obesity biomarker concentrations in
33
34 16 middle-aged men and women. *Diabetologia* 2011; 54: 1676-1683.
35
36 17 45. Murphy N, Cross AJ, Abubakar M et al. A Nested Case-Control Study of Metabolically
37
38 18 Defined Body Size Phenotypes and Risk of Colorectal Cancer in the European Prospective
39
40 19 Investigation into Cancer and Nutrition (EPIC). *PLoS Med* 2016; 13: e1001988.
41
42 20 46. Aleksandrova K, Boeing H, Jenab M et al. Metabolic syndrome and risks of colon and
43
44 21 rectal cancer: the European prospective investigation into cancer and nutrition study. *Cancer*
45
46 22 *Prev Res (Phila)* 2011; 4: 1873-1883.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 47. Aleksandrova K, Jenab M, Boeing H et al. Circulating C-reactive protein concentrations
4
5
6 2 and risks of colon and rectal cancer: a nested case-control study within the European Prospective
7
8 3 Investigation into Cancer and Nutrition. *Am J Epidemiol* 2010; 172: 407-418.
9
10 4 48. Aleksandrova K, Boeing H, Jenab M et al. Total and high-molecular weight adiponectin
11
12 5 and risk of colorectal cancer: the European Prospective Investigation into Cancer and Nutrition
13
14 6 Study. *Carcinogenesis* 2012; 33: 1211-1218.
15
16
17 7 49. Wei EK, Ma J, Pollak MN et al. C-peptide, insulin-like growth factor binding protein-1,
18
19 8 glycosylated hemoglobin, and the risk of distal colorectal adenoma in women. *Cancer Epidemiol*
20
21 9 *Biomarkers Prev* 2006; 15: 750-755.
22
23
24 10 50. Murphy N, Cross AJ, Huang WY et al. A prospective evaluation of C-peptide levels and
25
26 11 colorectal adenoma incidence. *Cancer Epidemiol* 2015; 39: 160-165.
27
28
29 12 51. Giovannucci E, Pollak MN, Platz EA et al. A prospective study of plasma insulin-like
30
31 13 growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer*
32
33 14 *Epidemiol Biomarkers Prev* 2000; 9: 345-349.
34
35
36 15 52. Xu XT, Xu Q, Tong JL et al. Meta-analysis: circulating adiponectin levels and risk of
37
38 16 colorectal cancer and adenoma. *J Dig Dis* 2011; 12: 234-244.
39
40
41 17 53. Gialamas SP, Sergentanis TN, Antonopoulos CN et al. Circulating leptin levels and risk
42
43 18 of colorectal cancer and adenoma: a case-control study and meta-analysis. *Cancer Causes*
44
45 19 *Control* 2013; 24: 2129-2141.
46
47
48 20 54. Kim JH, Lim YJ, Kim YH et al. Is metabolic syndrome a risk factor for colorectal
49
50 21 adenoma? *Cancer Epidemiol Biomarkers Prev* 2007; 16: 1543-1546.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 55. Kang HW, Kim D, Kim HJ et al. Visceral obesity and insulin resistance as risk factors for
4
5
6 2 colorectal adenoma: a cross-sectional, case-control study. *Am J Gastroenterol* 2010; 105: 178-
7
8 3 187.
9
10 4 56. Adelstein BA, Macaskill P, Chan SF et al. Most bowel cancer symptoms do not indicate
11
12 5 colorectal cancer and polyps: a systematic review. *BMC Gastroenterol* 2011; 11: 65.
13
14
15 6 57. Klipstein-Grobusch K, Kroke A, Boeing H. Reproducibility of self-reported past body
16
17 7 weight. *Eur J Clin Nutr* 1998; 52: 525-528.
18
19
20 8 58. Stevens J, Keil JE, Waid LR, Gazes PC. Accuracy of current, 4-year, and 28-year self-
21
22 9 reported body weight in an elderly population. *Am J Epidemiol* 1990; 132: 1156-1163.
23
24
25 10 59. Dahl AK, Reynolds CA. Accuracy of recalled body weight--a study with 20-years of
26
27 11 follow-up. *Obesity (Silver Spring)* 2013; 21: 1293-1298.
28
29
30
31
32 12
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **1 Figure Legends.**
4

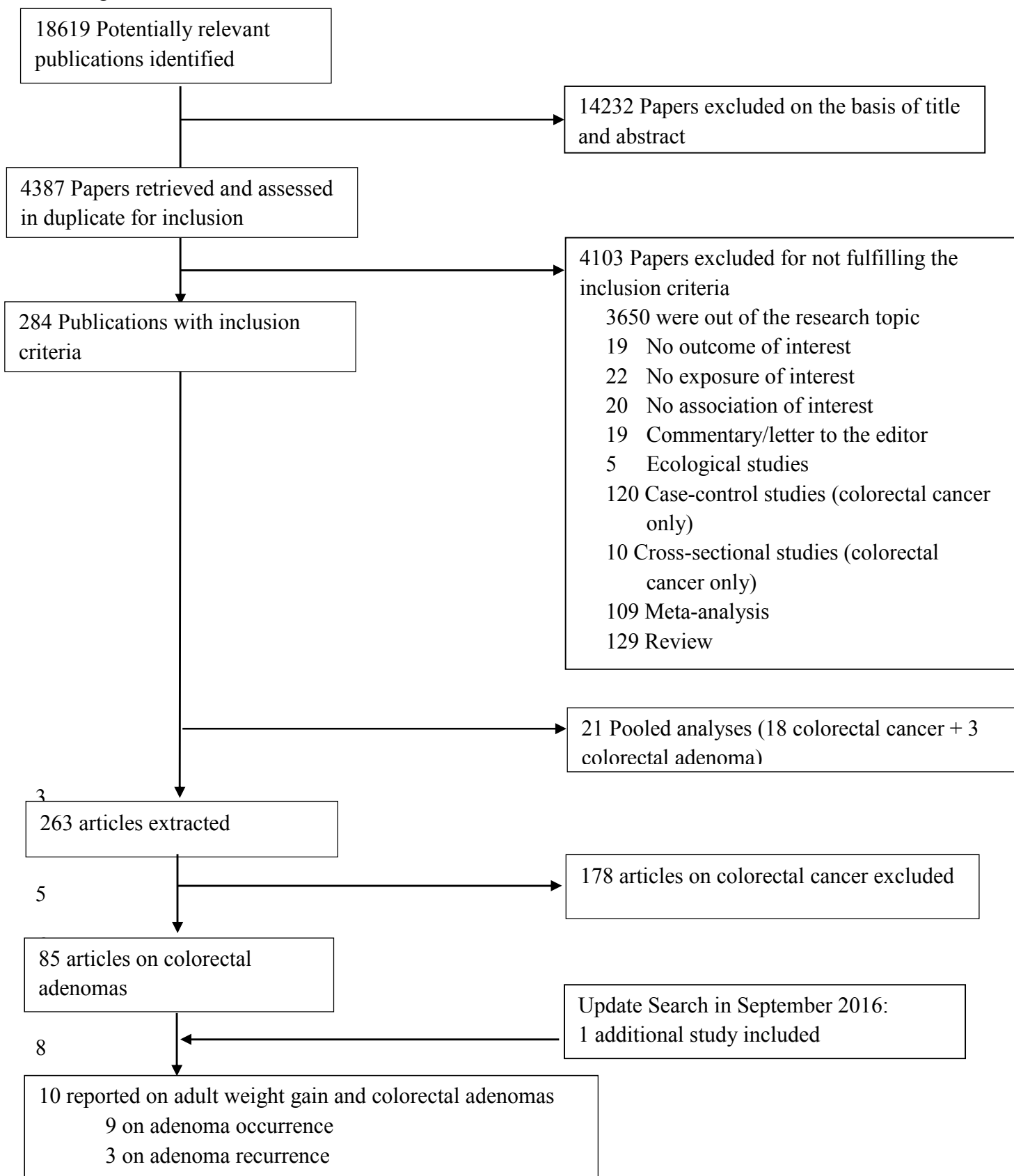
5
6 2 Figure 1: Flow chart of study selection
7

8 3 Figure 2: High vs low meta-analysis for weight gain and colorectal adenoma occurrence and
9
10 4 recurrence
11

12 5 Figure 3: Dose-response meta-analysis for weight gain per 5 kg and colorectal adenoma
13
14 6 occurrence
15
16

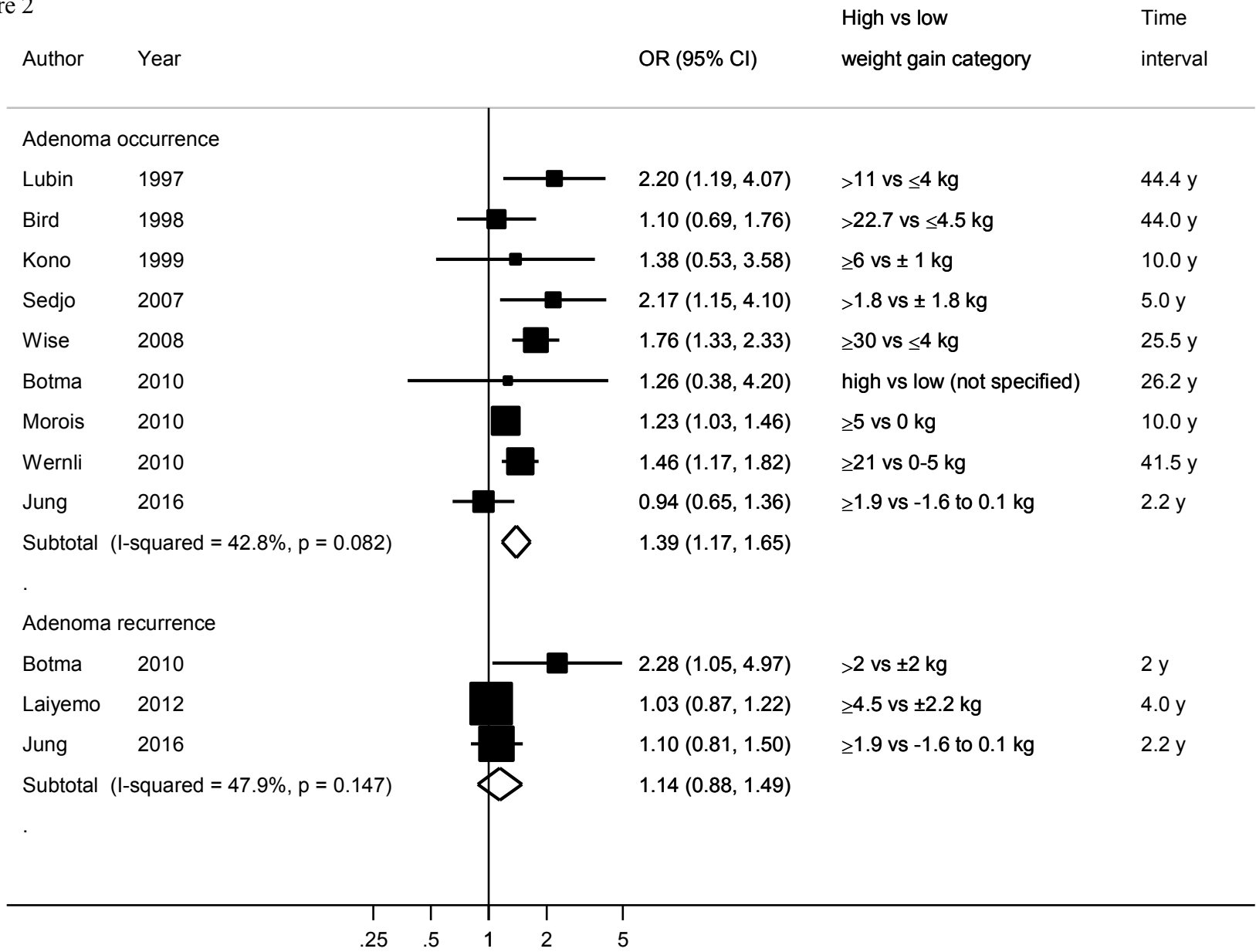
17 7 Figure 4: Non-linear dose-response meta-analysis for weight gain and colorectal adenoma
18
19 8 occurrence ($P_{non-linearity} < 0.001$)
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Figure 1



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Figure 2



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

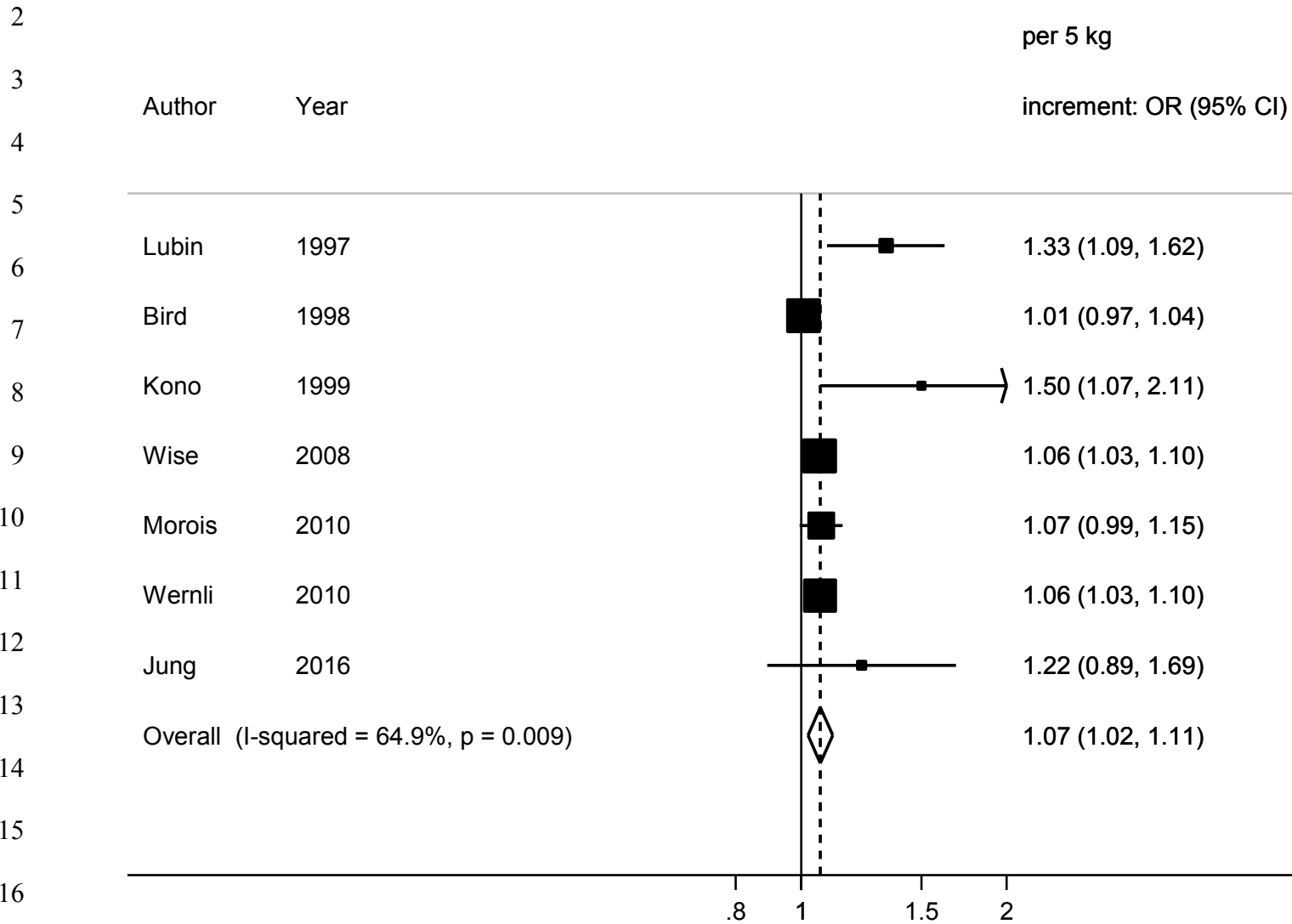
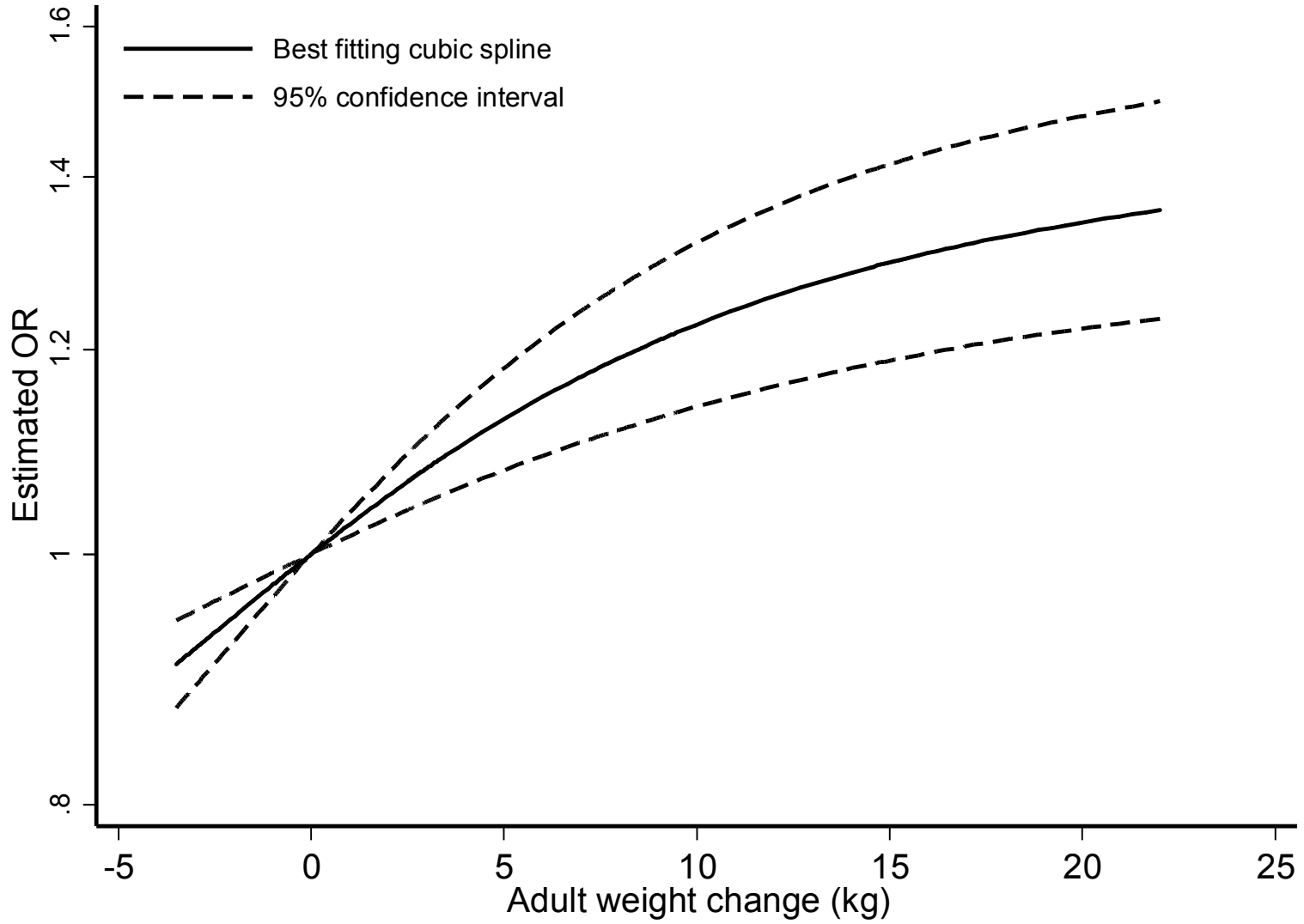
1
2
3 Figure 3
4

Figure 4.



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Table 1. Characteristics of the included studies

Author, year (country)	Study source, study design, (follow-up)	Sex, Age	Outcome, Outcome assessment	Sample size, N cases, controls	Exposure assessment	Exposure categories	Relative Risk (95% CI)	Adjustment
Retrospective studies								
Lubin 1997 (Israel)[25]	Screening Program of the gastroenterology Department at the Tel Aviv Medical Center, Retrospective study	M & F, 21-75 y	colorectal adenomas, colonoscopy	cases: 196 controls: 196	self-reported baseline weight and recalled weight at age 18	<4 kg (ref), 4-11 kg, >11 kg	<4: 1 4-11: 1.5 (1.1-2.1) >11: 2.2 (1.2-4.1)	total energy and physical activity
Bird, 1997 (US)[20]	Screening at Southern California Kaiser Permanente medical centers, Retrospective study	M & F, 50-75 y	colorectal adenomas, sigmoidoscopy	cases: 483 controls: 483	self-reported baseline weight and recalled weight at age 18	Quartiles: Q1:-34.1-4.5 kg (ref) Q2:>4.5-13.6 kg Q3:>13.6-22.7 kg Q4:>22.7-81.8 kg	Q1: 1 Q2: 1.0 (0.7-1.5) Q3: 1.1 (0.7-1.7) Q4: 1.1 (0.7-1.8)	sex, age, date sigmoidoscopy, center, BMI
Kono, 1999 (Japan)[21]	Health examination at the Japan Self Defence Forces, Retrospective study	M, 47-55 y	colon adenomas, colonoscopy	cases: 189 controls: 226	measured baseline weight and recorded weight 10 y before	≤ -2 kg (ref) -1-1kg 2-5 kg ≥ 6kg	≤ -2: 1 -1-1: 1.6 (0.9-2.7) 2-5: 1.8 (1.0-3.0) ≥ 6: 2.2 (1.0-4.8)	hospital, rank in the self-defence force, smoking, alcohol use
Wernli, 2010 (US)[29]	Group Health, Retrospective study	M & F, 20-74 y	colorectal adenomas, colonoscopy	colon: 519 rectum: 691 both: 227 controls: 772	self-reported recalled weight 1y before colonoscopy and at age 18 y	weight loss 0-5 kg 6-10 kg 11-20 kg >21 kg	Colon: weight loss: 1.03 (0.60-1.78) 0-5 kg: 1 6-10 kg: 1.23 (0.83-1.82) 11-20 kg: 1.18 (0.84-1.66) >21 kg: 1.41 (0.99-2.02) Rectum: weight loss: 1.26 (0.78-2.03) 0-5 kg: 1 6-10 kg: 1.37 (0.96-1.96) 11-20 kg: 1.28 (0.94-1.75) >21 kg: 1.29 (0.93-1.80) Both lesions: weight loss: 1.22 (0.54-2.74) 0-5 kg: 1 6-10 kg: 1.34 (0.74-2.44) 11-20 kg: 1.90 (1.15-3.14)	age, sex, race, education, smoking status, alcohol intake, NSAID use, family history of CRC, menopausal status, hormone use

>21 kg: 2.16 (1.28-3.63)

Laiyemo, 2012 (US)[24]	Polyp Prevention Trial, Retrospective study, 4 y	M & F, 61.0 y	colorectal adenoma recurrence, colonoscopy	N: 1,826 Recurrence: 723	measured weight at baseline and after 4 y (at diagnosis of recurrence)	loss ≥ 10 lbs loss (5-9 lbs) no change (ref) 5-9 lbs ≥10 lbs	≤-10 lbs: 0.91 (0.77-1.07) -5- -9 lbs) 0.90 (0.76-1.07) no change: 1 (ref) 5-9 lbs: 0.97 (0.82-1.16) ≥10 lbs: 1.03 (0.87-1.23)	age, sex, NSAID use, smoking status, baseline weight, dietary randomized assignment, family history of CRC
------------------------	--	---------------	--	-----------------------------	--	---	---	--

Adenomas:

All:

Q1: 1

Q2: 1.24 (0.95-1.63)

Q3: 1.28 (0.98-1.66)

Q4: 1.17 (0.89-1.53)

Men:

Q1: 1

Q2: 1.31 (0.98-1.74)

Q3: 1.31 (0.98-1.74)

Q4: 1.25 (0.94-1.67)

Women:

Q1: 1

Q2: 0.84 (0.38-1.88)

Q3: 1.11 (0.53-2.31)

Q4: 0.62 (0.25-1.51)

Recurrence:

All:

Q1: 1

Q2: 1.17 (0.93-1.47)

Q3: 1.25 (0.98-1.58)

Q4: 1.29 (1.02-1.64)

Men:

Q1: 1

Q2: 1.15 (0.91-1.46)

Q3: 1.28 (1.00-1.64)

Q4: 1.31 (1.03-1.67)

Women:

Q1: 1

Q2: 1.23 (0.51-2.99)

Q3: 1.20 (0.46-3.17)

Q4: 1.23 (0.45-3.36)

Jung, 2016 (Korea)[23]	Health screening program at Kangbuk Samsung Hospital, Retrospective study, 2.2 y	M & F, 41.2 y	colorectal adenomas and recurrence, colonoscopy	N: 3,121 without and 2,176 with adenoma Cases: 447 Recurrence: 591	measured weight at baseline and after 2.2 y (at diagnosis of adenoma or recurrence)	Quartiles: Q1:<-1.6 kg (ref) Q2-1.6-0.1 kg Q3:0.2-1.8 kg Q4:≥ 1.9 kg	Age, sex, smoking status, family history of CRC, NSAID use, baseline weight
------------------------	--	---------------	---	---	---	--	---

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Prospective studies

Sedjo, 2007 (US)[26]	Insulin Resistance Atherosclerosis Study, Prospective study, ~5y	M & F, mean age 64 y	colorectal adenomas, colonoscopy	N: 600 cases: 136	measured baseline weight and prospective weight after 5 y	≤ -4 pounds -4-4 pounds (ref) >4 pounds	≤-4: 1.52 (0.60-3.87) 4-4: 1 >4: 2.17 (1.15-4.11)	age, sex, clinic, ethnicity, smoking, estimated energy expenditure, previous polyp history, baseline BMI
Wise, 2008 (US)[27]	Black Women's Health Study Prospective study, 6.3 y	F, mean 43.5 y	colorectal adenomas , self-reported	N: 33,403 Cases: 1,189	self-reported baseline weight and recalled weight at age 18	<5 kg (ref), 5-14 kg 15-29 kg ≥30 kg	<5 kg: 1 5-14 kg: 1.44 (1.09-1.91) 15-29 kg: 1.57 (1.20-2.06) ≥30 kg: 1.76 (1.33-2.33)	Age, questionnaire cycle, physical activity, family history of colorectal cancer, smoking, education, nonsteroidal anti- inflammatory drug use, menopausal status, postmeno- pausal hormone use, red meat intake, fiber intake, energy, BMI at age 18
Botma, 2010 (The Netherlands)[2 2]	GEOLynch study (MMR gene mutation carrier), Prospective study, 1.7 y	M & F, 44.2 y	colorectal adenomas and recurrence, colonoscopy	N: 243 Cases: 22 Recurrence: 36	self-reported baseline weight and recalled weight at age 18 (for occurrence), and after 2 y (for recurrence)	For occurrence: grouped by median (not specified), for recurrence: ± 2 kg >2 kg	Adenomas: Men: low 3.60 (0.38-34.28) Women: 0.83 (0.20-3.48) Recurrence: Men: ± 2 kg: 1 >2 kg: 1.73 (0.67-4.45) Women: ± 2 kg: 1 >2 kg: 4.09 (1.04-16.19)	age, sex, smoking status, alcohol intake

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Morois, 2010 (France)[28]	E3N-EPIC-study – France, Prospective study, 2 y	F, mean 53.1 y	Colon and rectum adenomas, colonoscopy	N: 17,391 cases: 1,408	self-reported weight at baseline and self- reported prospective weight every 2 y	<0 kg/year 0 (ref) kg/year 0.1-0.49 kg/year ≥ 0.5 kg/year	<0: 1.12 (0.92-1.35) 0 (ref) 0.1-0.49: 1.25 (1.05-1.49) ≥ 0.5: 1.23 (1.03-1.46)	energy intake, alcohol intake, total physical activity, smoking status, CRC in first degree relatives, educational level, menopausal status, use of menopausal hormone therapy
------------------------------	--	----------------------	---	---------------------------	---	--	--	---

BMI, body mass index; CRC, colorectal cancer, F, female; M, male; NSAID, non-steroidal anti-inflammatory drugs; N, number; Y, year

1

Table 2. Summary odds ratio (OR) and 95% confidence intervals (95% CI) of high versus low meta-analyses of weight gain and occurrence of colorectal adenomas by subgroups

	Summary RR (95% CI)	N	I ² (%)	P _{within} ^a	P _{between} ^b
All studies	1.39 (1.17-1.65)	9	43	0.08	
Study design					
Prospective	1.37 (1.05-1.80)	5	61	0.04	0.78
Retrospective	1.45 (1.19-1.76)	4	3	0.38	
Sex					
Men	1.05 (0.71-1.55)	3	0	0.43	0.51
Women	1.36 (1.01-1.83)	4	49	0.12	
Site of adenoma					
Colon	1.27 (1.07-1.51)	3	0	0.80	0.73
Rectum	1.20 (0.93-1.55)	2	0	0.49	
Time of weight assessment					
Early adulthood	1.40 (1.10-1.77)	6	51	0.07	0.93
Mid-life adulthood	1.40 (1.00-1.95)	3	30	0.24	
Definition of high weight gain category					
<10 kg	1.24 (0.95-1.63)	4	42	0.16	0.21
≥ 10 kg	1.55 (1.26-1.90)	4	31	0.05	
Geographic area					
Asia	1.36 (0.76-2.45)	3	64	0.06	0.61
Europe	1.23 (1.04-1.46)	2	0	0.97	
USA	1.54 (1.26-1.89)	4	28	0.25	
Reference category					
Weight loss included	1.59 (1.19-2.12)	4	26	0.26	0.32
Stable weight	1.30 (1.07-1.58)	5	42	0.14	
Outcome assessment					
Colonoscopy	1.36 (1.12-1.65)	7	38	0.14	0.47
Sigmoidoscopy	1.10 (0.69-1.76)	1	-	-	
Self-reported	1.76 (1.33-2.33)	1	-	-	
Indication					
Without indication	1.40 (1.11-1.76)	7	56	0.04	0.92
With indication	1.45 (1.17-1.81)	2	0	0.81	
Adjustment for weight, BMI, waist circumference					
Yes	1.33 (1.06-1.67)	6	54	0.06	0.59
No	1.47 (1.23-1.76)	3	0	0.96	
Adjustment for physical activity					
Yes	1.51 (1.20-1.90)	4	55	0.08	0.25
No	1.25 (1.02-1.52)	5	10	0.35	
Adjustment for smoking status					
Yes	1.38 (1.15-1.66)	7	45	0.09	0.85
No	1.35 (1.01-1.80)	2	11	0.29	

Adjustment for alcohol intake

Yes	1.31 (1.15-1.50)	4	0	0.70	0.78
No	1.40 (1.06-1.85)	5	60	0.04	

Adjustment for family history colorectal cancer

Yes	1.34 (1.08-1.65)	4	65	0.03	0.68
No	1.44 (1.14-1.82)	5	0	0.57	

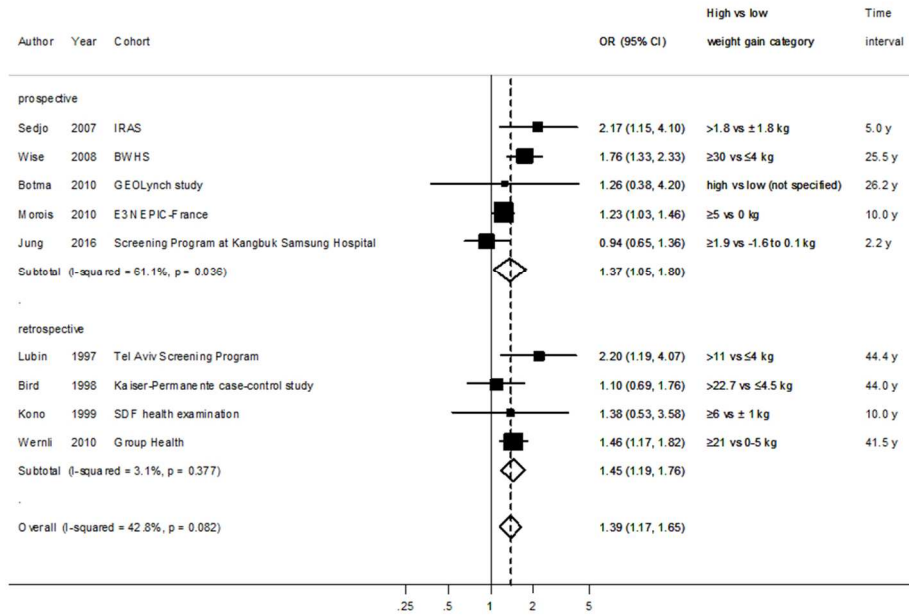
^a P_{within} , P for heterogeneity within each subgroup

^b $P_{between}$, P for heterogeneity between subgroups with meta-regression

1

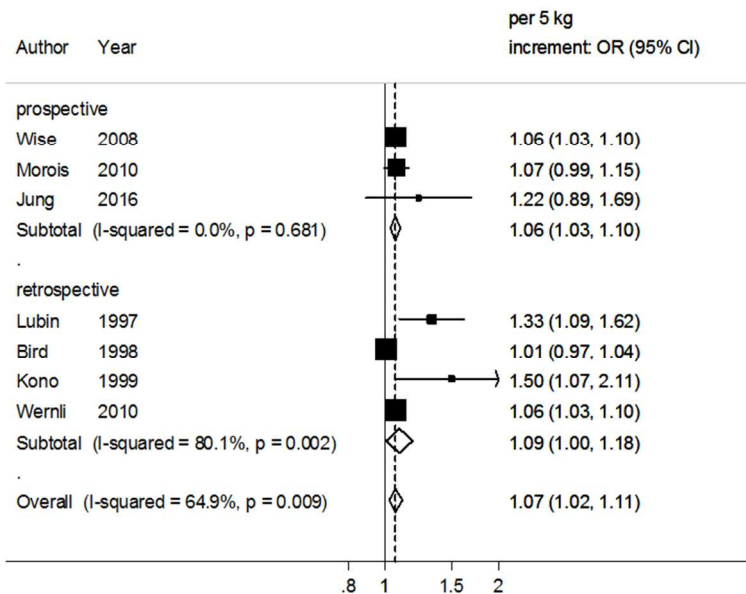
2

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



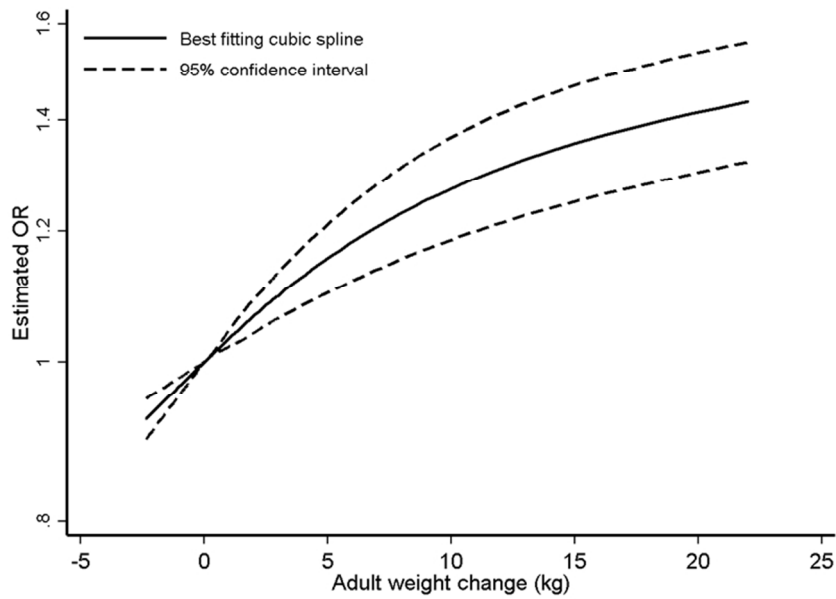
Supplementary figure S1: High vs low meta-analysis for weight gain and adenoma occurrence stratified by study design (p for heterogeneity by study design=0.78)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



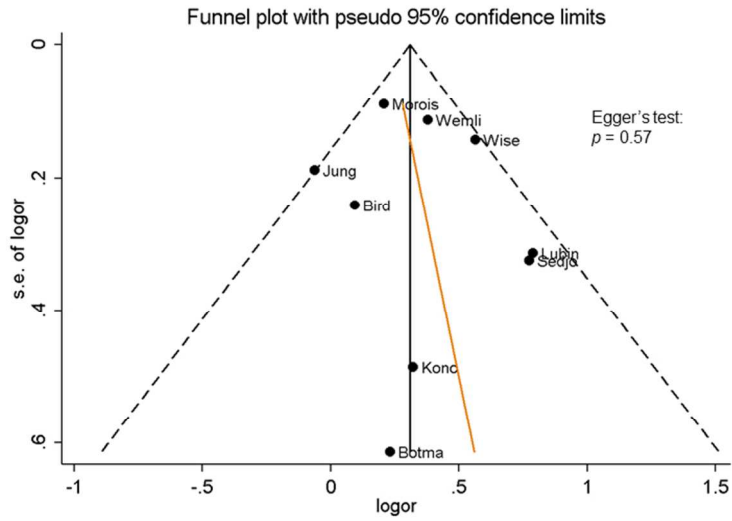
Supplementary figure S2: Dose-response meta-analysis for weight gain per 5 kg and adenoma occurrence stratified by study design (p for heterogeneity by study design=0.78)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Supplementary figure S3: Non-linear dose-response meta-analysis for weight gain and adenoma occurrence, only including prospective studies ($n=3$ studies; p non-linearity <0.001)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Supplementary figure S4: Funnel plot of studies included in the high vs low meta-analyses of weight gain and adenoma occurrence

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60