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Burden of long-term conditions and management of people with overweight and obesity: Data from the United Kingdom primary care cohort of the IMPACT-O study

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Abstract

Aims: The multi-country epidemiology landscape Patient Care pathways of Obesity (IMPACT-O) retrospective cohort study utilised existing electronic medical records to gather data on overweight and obesity. We report UK data on obesity-related complications (ORCs) and management strategies.

Materials and Methods: The UK IQVIA Medical Research Database, The Health Improvement Network database, includes routine data from UK primary care. Outcomes analysed included sociodemographic and clinical characteristics, ORCs and treatments for three cohorts: adults (≥ 18 years) with a new record of overweight or obesity (body mass index [BMI] ≥ 25 kg/m²; overweight/obesity cohort) or obesity (BMI ≥ 30 kg/m²; obesity cohort) identified by BMI recordings and/or diagnosis codes, and adults with ≥ 1 recorded interventions with an effect on weight (intervention cohort) between 2018 and 2022.

Results: There were 73 279 adults in the overweight/obesity cohort, 62 226 adults in the obesity cohort and 343 755 adults in the intervention cohort. Most adults had ≥ 1 ORC with a numerically higher proportion of ORCs recorded in the obesity cohort (58.4%) than in the overweight/obesity cohort (48.0%). For the intervention cohort, 77.0% had ≥ 1 ORC. Lifestyle interventions were recorded for 96.8% of this cohort, followed by pharmacological therapies with an effect on weight (glucagon-like peptide-1 receptor agonists, 3.6%; orlistat, 2.5%), and bariatric surgery (0.3%).

Conclusions: Results confirm the high burden of ORCs in adults at first identification of overweight or obesity in primary care and the limited use of pharmacotherapy and

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Plain Language Summary

- Health-related information recorded in electronic medical records during visits to your doctor can help increase understanding of the impact of overweight and obesity in healthcare settings.

- The epldeMiology landscape and PATient Care paThways of Obesity (IMPACT-O) was a study conducted in selected countries in Europe and the Asia-Pacific region that used information from existing healthcare records to report the impact of overweight and obesity. This paper reports the results from the UK part of the study, using information provided by general practitioners.
- Data on social, demographic and health-related characteristics of people with overweight and obesity were collected for adults (at least 18 years of age) at the time their first record of overweight or obesity was recorded, either with a diagnosis from the doctor or a body mass index (BMI) of $\geq 25 \text{ kg/m}^2$ (overweight/obesity group) or $\geq 30 \text{ kg/m}^2$ (obesity group) and for adults with at least one record indicating the use of a method for weight loss (intervention cohort).

- Most adults included in the study had at least one additional condition that was related to their obesity, and more people in the obesity group than the overweight/obesity group had an additional obesity-related condition. The most commonly recorded additional obesity-related condition was high blood pressure in the obesity group and depression in the overweight/obesity group.
- In the group who had a method of weight loss recorded, three in every four adults had at least one additional obesity-related condition. The average BMI of adults in this group was 29.0 kg/m². Lifestyle changes, such as diet and exercise, were recorded for nearly all adults in this group, followed by medications with an effect on weight (such as glucagon-like peptide-1 receptor agonists and orlistat), and weight-loss surgery.

- The study results confirm that adults are already heavily affected by obesity-related conditions by the time of their first formal documentation of overweight or obesity in primary care. Only a small number of adults with overweight or obesity had records of medication or surgery for weight loss management. These results mean that there is a need for improved surveillance of these adults in the UK.

body mass index, obesity, obesity-related complications, overweight, weight management

Obesity is a chronic relapsing disease associated with the excess accumulation of adipose tissue and adverse health effects.^{1,2} The World Obesity Federation estimates that by 2030, 1.25 billion adults globally will have

obesity, and 50% of all adults globally will have overweight or obesity.³ Data from various countries in the UK reported during 2019–2023 suggest that 26%–35% of adults had obesity, and 26%–38% had overweight.^{4–6}

Obesity-related complications (ORCs) include multiple diseases, such as cardiovascular disease, type 2 diabetes (T2D), sleep apnoea

and certain malignancies, which are associated with increased risk of all-cause mortality.⁷⁻¹² The burden of ORCs increases with increasing obesity class,¹³ with people at higher BMIs typically having multiple long-term conditions (MLTC or multimorbidity; ≥ 2 ORCs). In addition to ORCs, obesity negatively impacts health-related quality of life and healthcare utilisation.^{14,15}

The UK National Institute for Health and Care Excellence (NICE) recommends a tiered treatment approach for overweight and obesity, delivered by a multi-disciplinary weight management team. Tier 2 interventions include lifestyle interventions (such as diet, exercise and behavioural therapy), with these recommended for people with overweight (body mass index [BMI] ≥ 25 – 30 kg/m²); Tier 3 interventions include obesity management medications (OMM), prescribed for people with overweight and specified ORCs or obesity (BMI ≥ 30 kg/m²).^{16,17} Current pharmacological interventions approved for weight loss in adults in the UK, and recommended by NICE guidelines, include orlistat and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) liraglutide 3 mg and semaglutide 2.4 mg.¹⁶ While tirzepatide was approved for weight loss in the UK in November 2023, it is currently under NICE review.^{18,19}

Bariatric surgery is a Tier 4 intervention reserved for people with Class 3 obesity (BMI ≥ 40 kg/m²) or Class 2 obesity (BMI ≥ 35 to <40 kg/m²) and specified ORCs such as T2D.^{16,20} Despite the availability of treatment options, obesity prevalence is expected to rise in the coming years.³ Further studies are needed to understand treatment patterns and identify barriers to treatment.²¹

Data routinely recorded in electronic medical records (EMR) can aid in the understanding of the overweight and obesity impact in real-world settings. Primary care data provide an opportunity to understand chronic weight management strategies, which remain partially unexplored in the UK, and help identify potential targets for improvement. The epldeMiology landscape and PATient Care paThways of Obesity (IMPACT-O) multi-country retrospective cohort study utilised existing healthcare databases to report the extent of recording and impact of overweight and obesity, across selected countries in Europe and the Asia-Pacific region, including collecting data on the sociodemographic and clinical characteristics of people with overweight and obesity in these databases. The study found that BMI was recorded for 38.9% of active patients ($n = 4\,454\,982$) in the UK database. Of the 1 110 830 people identified with overweight or obesity (based on BMI recording and/or diagnosis codes in their EMR) only a small proportion (4.2%) had a diagnosis code present.^{22,23} Furthermore, the IMPACT-O study found that 71.2% of adults in the database had at least one ORC, with cardiometabolic ORCs occurring most commonly.²³

Here we present further analyses of data from the IMPACT-O study describing the sociodemographic and clinical characteristics, burden of ORCs, treatments and interventions of newly identified adults with a first record of overweight or obesity and adults with overweight or obesity and at least one record of an intervention with an effect on weight during the period 2018–2022 in the primary care setting in the UK, to support the limited existing literature and provide evidence to improve the management of overweight and obesity treatment.

2 | MATERIALS AND METHODS

2.1 | Study design

The IMPACT-O study was a multi-country retrospective observational cohort study that utilised existing healthcare databases such as EMR and claims databases standardised to the Observed Medical Outcomes Partnership (OMOP) Common Data Model from Australia, France, Germany, Italy, Spain, the UK and Japan. The methodology for the IMPACT-O study and multi-country results have been previously described.²³ This analysis reports data from the UK IQVIA Medical Research Data (IMRD) The Health Improvement Network (THIN) database for the study period 1 January 2018 to 30 September 2022.

All analyses in this study were conducted in accordance with Data Use Agreement terms as specified by the data owners. For the UK database, there was no Institutional Review Board applicable to the usage and dissemination of the results of this study or required registration of the protocol with additional ethics oversight.

2.2 | Database

The UK IMRD THIN is a database of anonymised EMR collected at primary care clinics throughout the UK. The database includes data from 13.7 million patients (20% of the UK population) with 842 general practitioner (GP) practices contributing to the database. Dates of service include 1994 through to the present.

Diagnoses and procedures were based on the presence of Systematised Nomenclature of Medicine (SNOMED) codes and prescriptions were captured as READ codes and gemscript (OMM data are recorded as prescriptions). The IMRD THIN database contains referral data, including referrals to radiologists, health trainers, orthopaedic services and surgeons.

Quality indicators defined the start date of each patient; each patient's observation period began at the latest of the patient's registration date, the acceptable mortality recording date of the practice or the date of the data collected in the system. The end of the observation period was determined by the end date of registration in the database.

2.3 | Population

This analysis focuses on three cohorts: (1) the overweight or obesity (overweight/obesity) cohort; (2) the obesity cohort; and (3) the intervention cohort. The overweight/obesity cohort included people with overweight or obesity based on BMI and/or diagnosis codes with 12 months of follow-up. The index date was the individual's first record, in the study period, of either a diagnosis code or BMI that defined overweight or obesity. People (≥ 18 years of age at index) with ≥ 1 BMI record ≥ 25 kg/m² and/or diagnosis code of overweight or obesity and ≥ 12 months follow-up pre- and post-index date were included. People with missing age or gender, BMI < 25 kg/m² 30 days

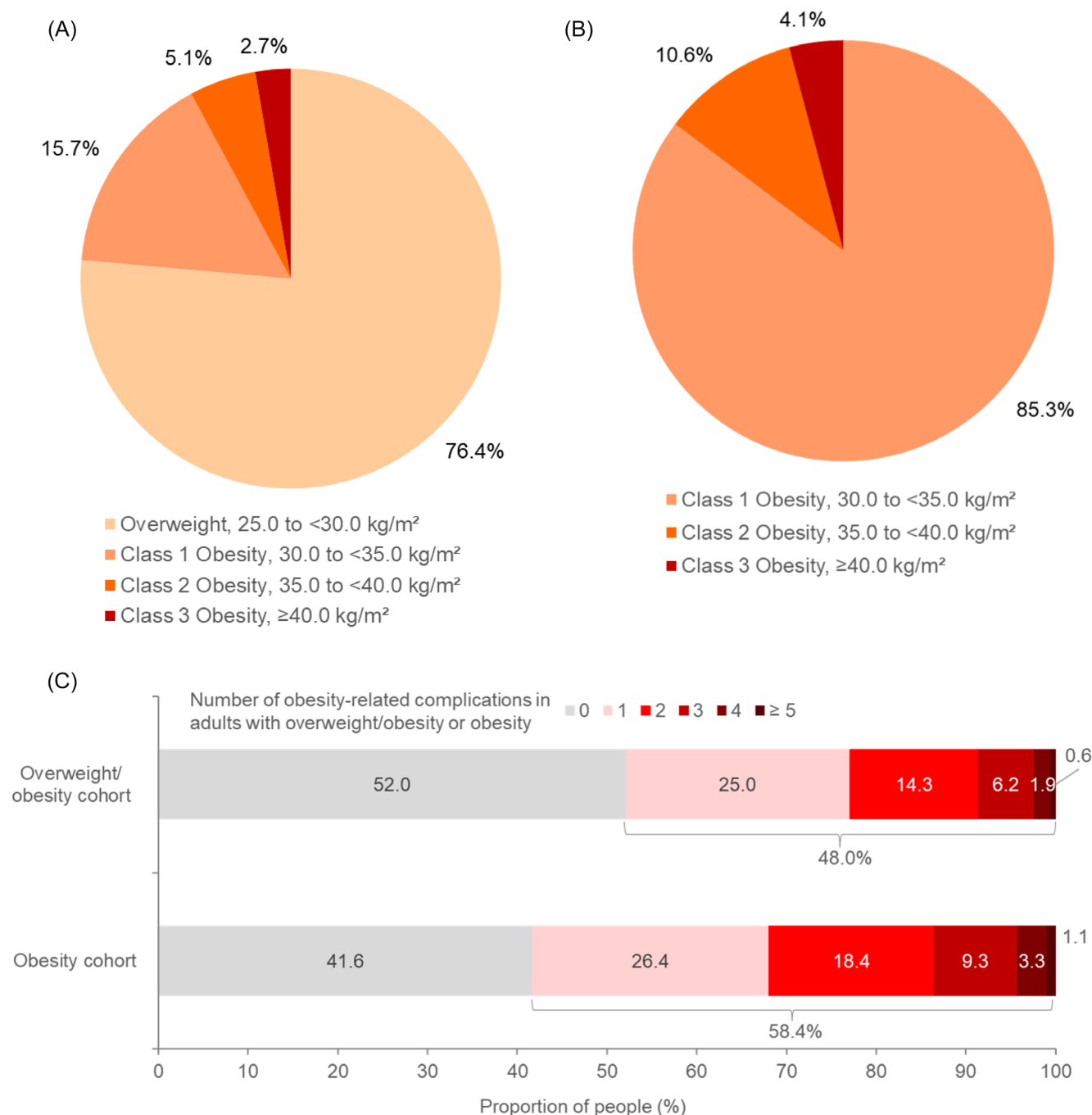


FIGURE 1 Body mass index (BMI) categories for people in the overweight/obesity cohort (A) and the obesity cohort (B) and number of obesity-related complications (C).

pre- and post- index date and/or BMI ≥ 30 kg/m² any time pre-index date were excluded (Figure 1A).

The obesity cohort included people with obesity based on BMI and/or diagnosis codes with 12 months follow-up. The index date was the individual's first record, in the study period, of either a diagnosis code or BMI which defined obesity. People (≥ 18 years of age at index) with ≥ 1 BMI record ≥ 30 kg/m² and ≥ 12 months follow-up pre- and post-index date were included. People with missing age or gender, BMI < 30 kg/m² 30 days pre- and post-index date and/or BMI ≥ 30 kg/m² any time pre-index date were excluded (Figure S1A).

The intervention cohort consisted of individuals with at least one record of an intervention with an effect on weight during the study period. Interventions considered included records of lifestyle interventions, OMM and bariatric surgery; codes for these are detailed in Table S1. The index date was defined as a person's first record of an intervention with an effect on weight during the study period. People (≥ 18 years of age at index) with at least one record of an intervention with an effect on weight during the study period; at least one record of obesity (based on BMI and/or diagnosis codes) within 12 months pre- and post-index date; and ≥ 12 months follow-up pre- and post-index

hypertension (21.3%), dyslipidaemia (11.0%), anxiety (8.5%) and T2D (3.2%) (Table 1). Additional ORCs are detailed in Table S2.

The database captured available interventions with an effect on weight and showed that a low number of these treatments were recorded for adults the overweight/obesity and obesity cohorts (Table 2). The number of recorded lifestyle interventions was similar for both cohorts: diet therapy was 1.4% and 1.1%, exercise was 22.4% and 23.5%, and physical therapy was 2.6% for both the overweight/obesity and obesity cohorts respectively. Less than 1% of adults had a record of bariatric surgery in both cohorts. Orlistat was the most recorded OMM and it was prescribed more frequently for those in the obesity cohort (overweight/obesity: 0.4%; obesity: 0.9%). Less than 1% of adults were receiving GLP-1 RAs in both cohorts (Table 2).

Specialist referral was low for both cohorts, with 'other specialities' (which excludes radiologists, GPs, health trainers, orthopaedic services and surgeons) making up the majority (~3%) of the referrals, followed by GPs (1% for each cohort) (Table 2).

3.2 | Intervention cohort

People in the intervention cohort had a mean (SD) age of 60.4 (15.6) years and 54.7% were female. People in the OMM and bariatric surgery groups were younger than those in the lifestyle intervention group (mean age 53.8 and 45.5 years vs. 60.7 years), and those groups had a greater number of women (63.4% and 84.8% vs. 54.2%). Approximately one-third of people had overweight (35.3%) and 39.5% had obesity (Classes 1–3); the mean (SD) baseline BMI was 29.3 (6.3) kg/m² (Table 3).

Most people (77%) had ≥1 ORC; hypertension (60.5%) was the most frequently recorded ORC followed by dyslipidaemia (44.1%), depression (24.9%), T2D (20.1%) and anxiety (6.9%) (Table 3). There was a numerically greater proportion of people with MLTC (≥2 ORCs) in the OMM group than the lifestyle group (76.3% vs. 54.8%), but this was not the case for the bariatric surgery group (36%). Lifestyle interventions were recorded for nearly all people (96.8%) in this cohort followed by OMMs (GLP-1 RAs, 3.6%; orlistat, 2.5%) and bariatric surgery (0.3%). The frequency of prescriptions of OMM and bariatric surgery increased with obesity class (Figure 2).

4 | DISCUSSION

This study describes the sociodemographic and clinical characteristics, ORC burden and management of adults with a first record of overweight or obesity recorded and adults with overweight or obesity and at least one record of an intervention with an effect on weight in the UK IMRD THIN primary care database between 2018 and 2022.

All three cohorts had a high ORC burden, with 48.0%, 58.4% and 77.0% of the overweight/obesity, obesity and intervention cohorts having at least one ORC, respectively. People in the intervention cohort were older and had a higher cardiovascular risk profile as evidenced by the greater rates of hypertension and dyslipidaemia in the

TABLE 2 Interventions with an effect on weight and specialist referrals of people in the overweight/obesity cohort and the obesity cohort, 2018–2022.

	Overweight/obesity cohort (n = 73 279)	Obesity cohort (n = 62 226)
Interventions with an effect on weight ^a		
Pharmacological therapies with effects of weight		
GLP-1 receptor agonists	43 (0.1)	82 (0.1)
Orlistat	264 (0.4)	586 (0.9)
Bariatric surgery	20 (0.0)	37 (0.1)
Lifestyle intervention		
Diet therapy	1021 (1.4)	682 (1.1)
Exercise	16 437 (22.4)	14 629 (23.5)
Physical therapy ^b	1933 (2.6)	1645 (2.6)
Referral to specialist ^c		
Radiologist	<5 (0.0)	6 (0.0)
General practitioner	780 (1.1)	678 (1.1)
Health trainer	645 (0.9)	405 (0.7)
Orthopaedic service	27 (0.0)	28 (0.0)
Surgeon	109 (0.2)	86 (0.1)
Other specialties	2268 (3.1)	2164 (3.5)

Abbreviation: GLP-1, glucagon-like peptide-1.

^aIn the 12-month follow-up period.

^bPhysical therapy included: physiotherapy; therapeutic exercises to develop strength and endurance, range of motion and flexibility; weight control assessment; weight control behaviour observation; weight control education; and weight management classes.

^cAt index date.

intervention cohort than in the overweight/obesity and obesity cohorts. The presence of cardiometabolic ORC including hypertension and dyslipidaemia in adults with overweight or obesity aligned with findings of a meta-analysis that reported an association between obesity and adverse cardiovascular outcomes.²⁷ International obesity management guidelines agree on referring people with overweight and ORCs or obesity for specialist treatment.^{16,28–30} Thus, the profile of people in the intervention cohort is as expected, as their clinical profile meets the guideline requirements for treatment interventions. Of note, 20% of people in the intervention cohort had T2D. Since semaglutide and liraglutide were approved and available for the treatment of T2D during the study period, it is not possible to discern whether GLP-1 RA use, recorded in these people with T2D, was for the treatment of hyperglycaemia or weight loss or both.

Our study reports data on the first record of a formal overweight or obesity diagnosis in EMR. Most adults in our study had ≥1 ORC at the time of their first record of overweight or obesity. Although several explanations are possible (e.g., delayed BMI recording, physician coding behaviour), this observation could suggest diagnoses of overweight and obesity are driven by the presence of ORC rather than because of obesity. The ACTION-IO study reported that adults in the

TABLE 3 Baseline demographic and clinical characteristics of the intervention cohort according to interventions received.

Parameters	People receiving interventions with an effect on weight			
	Overall (n = 343 755)	Lifestyle intervention (n = 328 027)	OMMs (n = 15 474)	Bariatric surgery (n = 460)
Age at index date, mean (SD)	60.4 (15.6)	60.7 (15.6)	53.8 (14.0)	45.5 (12.6)
Gender, female, n (%)	187 895 (54.7)	177 817 (54.2)	9816 (63.4)	390 (84.8)
Baseline BMI ^a (kg/m ²), mean (SD)	29.3 (6.3)	29.0 (6.1)	38.0 (6.9)	39.6 (8.2)
BMI categories, n (%)				
<25.0 kg/m ²	81 331 (25.2)	81 225 (26.1)	92 (0.8)	14 (5.4)
≥25.0 kg/m ²	241 305 (74.8)	230 056 (73.9)	11 205 (99.2)	247 (95.0)
25.0 to <30.0 kg/m ²	113 822 (35.3)	112 869 (36.3)	953 (8.4)	14 (5.4)
30.0 to <35.0 kg/m ²	73 963 (22.9)	70 898 (22.8)	3079 (27.3)	41 (15.8)
35.0 to <40.0 kg/m ²	32 639 (10.1)	29 320 (9.4)	3306 (29.3)	68 (26.2)
≥40.0 kg/m ²	20 883 (6.5)	16 969 (5.5)	3869 (34.3)	124 (47.7)
Number of ORCs ^b				
0	79 086 (23.0)	77 533 (23.6)	1429 (9.2)	143 (31.1)
≥1	264 669 (77.0)	250 494 (76.4)	14 045 (90.8)	317 (68.9)
1	73 203 (21.3)	70 849 (21.6)	2240 (14.5)	147 (32.0)
2	89 217 (26.0)	86 588 (26.4)	2559 (16.5)	106 (23.0)
3	63 979 (18.6)	59 404 (18.1)	4581 (29.6)	53 (11.5)
4	27 665 (8.1)	24 436 (7.5)	3265 (21.1)	7 (1.5)
≥5	10 605 (3.1)	9217 (2.8)	1400 (9.1)	<5 (NR)
ORCs, ^c n (%)				
Hypertension	207 950 (60.5)	197 573 (60.2)	10 364 (67.0)	154 (33.5)
Dyslipidaemia	151 514 (44.1)	143 032 (43.6)	8530 (55.1)	60 (13.0)
Depression	85 615 (24.9)	77 844 (23.7)	7645 (49.4)	221 (48.0)
Anxiety	23 847 (6.9)	21 781 (6.6)	2040 (13.2)	51 (11.1)
T2D	68 973 (20.1)	59 876 (18.3)	9181 (59.3)	35 (7.6)
Baseline cardiometabolic parameters, mean (SD)				
HbA1c (%)	6.6 (1.5)	6.5 (1.5)	8.2 (2.0)	6.0 (1.1)
Total cholesterol (mg/dL)	87.5 (21.3)	87.6 (21.2)	80.7 (21.8)	81.8 (23.6)
Systolic blood pressure (mmHg)	132.0 (16.4)	131.9 (16.4)	133.4 (16.2)	127.9 (16.2)
Diastolic blood pressure (mmHg)	77.9 (10.2)	77.8 (10.2)	79.4 (10.2)	79.4 (11.1)

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; NR, not reported; OMM, obesity management medicines; ORCs, obesity related complications; SD, standard deviation; T2D, type 2 diabetes.

^aWithin ±60 days of the index date, closest to index date.

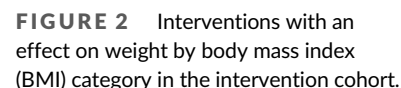
^bConsidering data on diagnosis and medication, at follow-up (within 1 year after the assessment date for overweight and obesity cohorts; within 1 year after the index date for the intervention cohort).

^cConsidering data on diagnosis and medication, at follow-up (within 1 year after index date).

UK wait an average of 9 years to discuss their weight issues with a healthcare provider.³¹ These results highlight the importance of educating physicians on the need for early diagnosis of overweight and obesity, before the onset of ORCs, to widen the window for lifestyle interventions and other treatment options.

The intervention cohort described weight loss management pathways of adults with overweight or obesity but not at first record of overweight or obesity. This approach allowed for learning how people with overweight or obesity are managed irrespective of the timing of their BMI records. Lifestyle intervention was the most common

intervention with an effect on weight recorded in this study, which falls within Tier 2 weight management.³² Records of pharmacotherapies with an effect on weight loss increased numerically with higher BMI category; this was also true for records of bariatric surgery. This aligns with the fact that obesity management is prioritised in adults with a higher severity of obesity and higher rates of ORCs (BMI and T2D or multimorbidity). Of note, NICE recommendations state that referral to tier 3 services should be considered in people with complex disease or situations where conventional treatment has been unsuccessful,¹⁶ but our results suggest that referrals to higher-tier



measurements in databases is very limited, the use of other anthropometric measures to identify people with obesity was not possible. Nevertheless, the objective was to describe what was available in these data sources, which is expected to reflect current clinical practices for overweight/obesity. Data were derived from people who visit primary care providers participating in the database. However, participating practices are thought to be representative of most obesity treatment practices within the UK. In addition, there was a lack of detailed sociodemographic data available in the database. Since this is a primary care database, under-recording of BMI and interventions with an effect on weight, especially bariatric surgery, is possible. OMM data are based on prescribed treatments only; we were unable to determine whether prescriptions were dispensed to/picked up by the patient. In addition, a lack of data on OMM dose in EMR meant determining whether these medications were used for T2D or weight loss in the 20% of people with T2D in the intervention group was not possible. For ORCs we used medications to identify certain conditions. However, we were unable to use this approach consistently for all relevant ORCs as some do not have specific treatments or were not specifically analysed for the purpose of the present study. Further, ORCs were only determined for a 1-year period before index, which would limit the identification of all ORCs for a given patient. Further analyses with longer pre-index periods are warranted. As this is a descriptive study, it was not designed to draw comparisons between cohorts. The observed differences described in this study should be interpreted with caution.

5 | CONCLUSION

The present analysis based on the UK cohort of the IMPACT-O study described sociodemographic and clinical characteristics, ORC burden,

treatment interventions and treatment pathways of people at first available record of overweight or obesity in primary care settings in the UK during 2018–2022. Our study confirms the high burden of ORC in adults with obesity, highlights the ORC burden in adults with overweight and the underutilisation of pharmacotherapy and bariatric surgery, despite the number of records of pharmacotherapies with an effect on weight and bariatric surgery increasing with increasing BMI class. The high burden of ORCs in this population of people receiving a first diagnosis of overweight or obesity suggests that the presence of ORCs may be prompting the diagnosis of overweight or obesity, and that there may be a delayed recognition of obesity in this setting. The lifestyle intervention data recorded in our study highlight the current treatment options offered to adults with overweight and obesity in the UK and contribute to the understanding of obesity treatment patterns in the UK primary care setting; these data could be used to inform efforts to improve the recording of diagnoses and management options of adults with overweight and obesity. Understanding barriers to treatment in primary care settings in the UK may improve access to earlier and more optimal treatment for people with overweight and obesity. Finally, the study highlights the importance of developing primary and secondary obesity prevention strategies that promote healthy lifestyle habits through public health campaigns and education, aiming to mitigate obesity-related health risks and reduce long-term healthcare costs for individuals and societies.

AUTHOR CONTRIBUTIONS

Lill-Brith von Arx, Alun Lloyd Davies and Esther Artime have made substantial contributions to the conception and design of the work, interpretation of data for the work and drafting of the work. Drafting of the work and critical revision of the work for important intellectual content. Kamlesh Khunti and Matt Capehorn have made substantial contributions to the interpretation of data for the work and critical revision of the work for important intellectual content. Atif Adam has made substantial contributions to the design and acquisition of data for the work, and critical revision of the work for important intellectual content. Anastasia Lampropoulou has made substantial contributions to the analysis and interpretation of data and critical revision of the work for important intellectual content. All authors have given final approval of this version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

Esther Artime, Lill-Brith von Arx and Alun Lloyd Davies are employees and shareholders of Eli Lilly and Company. Anastasia Lampropoulou is

a former employee and a former minor shareholder of Eli Lilly and Company. Atif Adam and Matt Capehorn have no conflicts of interest to declare. Kamlesh Khunti has acted as a consultant, speaker or received grants for investigator-initiated studies for Amgen, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Embecta, Eli Lilly and Company, MSD, Nestle Health Science, Novo Nordisk, Oramed Pharmaceuticals, Pfizer, Roche, Sanofi and Servier.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70345>.

DATA AVAILABILITY STATEMENT

All data relevant to the article are included in the main text or uploaded as Supporting Information S1.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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