

of the limited parameters that were measured in CNDMDS. This could have contributed to the difference in cluster characteristics (figure; appendix). However, these surrogates could be used as subgroup classification globally, since measurements for GADA and HbA<sub>1c</sub> might be unaffordable in developing countries. Additionally, this was a cross-sectional study and we only investigated the participants that had been newly diagnosed with diabetes, but not participants at the pre-diabetes stage or with diabetes of long disease duration. Thus, this data-driven cluster analysis only provides information about patients with new-onset disease and cannot provide information on long-term complications. To further test whether the clusters in our research shared the same clinical outcomes as the original European studies, prospective studies should be done. Our data provides a step towards a more precise diabetes stratification during epidemiological diabetes screening.

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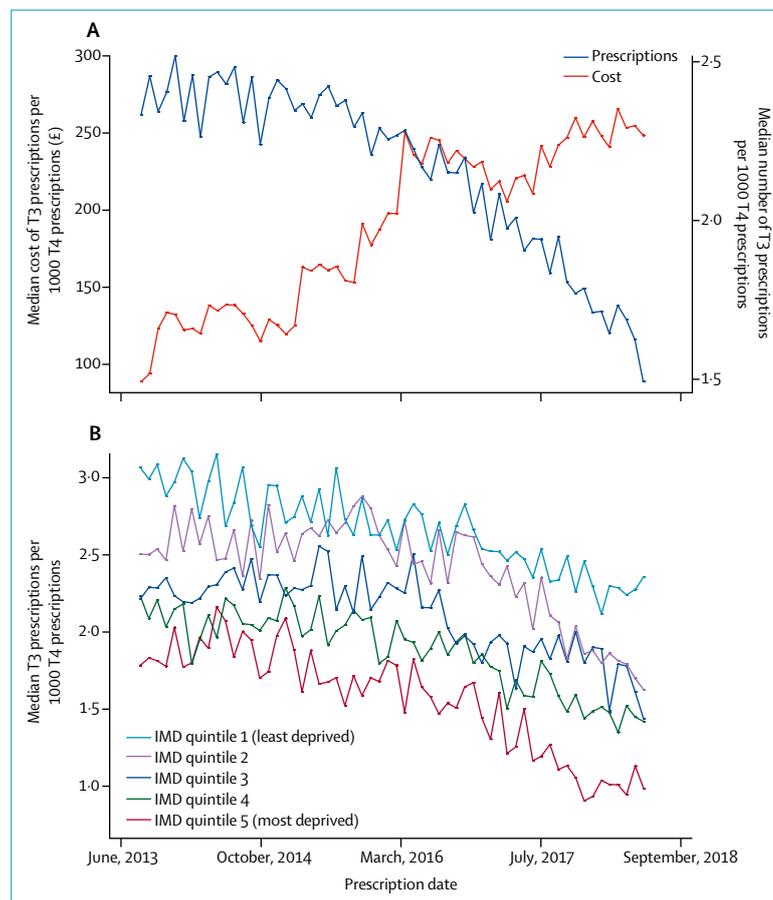
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## Liothyronine cost and prescriptions in England

Levothyroxine is commonly prescribed for hypothyroidism and its use is steadily increasing.<sup>1</sup> A subgroup of patients are dissatisfied on levothyroxine monotherapy<sup>2</sup> and in some clinical trial patients

have shown a preference for a combination of levothyroxine and liothyronine. With clinical trials not showing clear-cut superiority, combination thyroid hormone therapy remains controversial.<sup>3</sup> However, acknowledging the limitations (small size, short duration, inconsistent dosage) of previous studies, specialist society guidance recognises that a trial of liothyronine might be appropriate in selected patients<sup>4</sup> and studies of genetic polymorphisms (eg, Thr92AlaD2) might indicate specific patients to target. In 2016, the 28-day National Health Service (NHS) cost of liothyronine in the UK increased dramatically from about £4.50 to £258.19, resulting in widespread patient concern and media coverage.<sup>5</sup>



**Figure: Liothyronine costs and prescriptions in England, 2013–18**

(A) Total cost and number of liothyronine prescriptions per 1000 levothyroxine prescriptions. (B) Median number of liothyronine prescriptions per 1000 levothyroxine prescriptions by Index of Multiple Deprivation quintile. T3=liothyronine. T4=levothyroxine.

By contrast, the cost of levothyroxine has broadly remained the same. Clinicians are under increasing pressure to justify prescriptions and, for many patients, treatment has been discontinued or requires private sourcing. A parliamentary enquiry is ongoing. As these changes in costs occurred uniquely in the NHS, these trends in liothyronine prescribing likely only apply in the UK.

We analysed NHS England open prescribing data<sup>6</sup> from Aug 1, 2013, to July 1, 2018, sequentially examining the monthly number and cost of NHS liothyronine prescriptions for each clinical commissioning group (CCG; n=195). CCGs are responsible for commissioning health-care services in their local area. In August, 2013, the median number of monthly liothyronine prescriptions per CCG was 22 (IQR 12–38), falling to 17 (10–30) by July, 2018 ( $p<0.0001$ ). The most substantial changes in prescribing occurred in early 2016, coincident with substantial rise in costs (figure). The total monthly cost of liothyronine prescriptions in August, 2013, was £758 975; this figure increased by almost ten times to £7 018 679 by July, 2018, despite 122 CCGs prescribing less liothyronine.

Between August, 2013, and July, 2018, there was a median 37% reduction in the ratio of liothyronine prescriptions per 1000 levothyroxine prescriptions nationwide, with a maximum 32-times reduction in one CCG. Widespread variation by CCG is now apparent, with a 49-times difference in liothyronine prescriptions per 1000 levothyroxine prescriptions. Analysis of CCG demographics showed

that for each quintile increase in economic deprivation, liothyronine prescriptions were 0.21 SDs lower (95% CI 0.11–0.31;  $p<0.0001$ ). An overview of current liothyronine prescribing by CCG and changes from 2013–18 are shown in the appendix.

Over the period analysed, no major study or guideline has advocated a change in liothyronine prescribing. Thus, this substantial reduction in prescribing seems to have been largely driven by cost. In view of the concerns raised by patients, this large disparity between CCGs in prescribing liothyronine linked to deprivation status is difficult to justify. Moreover, patients in more affluent areas might be more able to source liothyronine by private prescription, further exacerbating the inequality.

Overall, current pricing of liothyronine has substantially reduced its prescription, engendered widespread variability in patients' access to it, and increased its overall cost to the NHS. Additionally, patients might have turned to alternate sources of thyroid hormone replacement such as Armour Thyroid (desiccated thyroid extract), which contains a supraphysiological ratio of tri-iodothyronine to thyroxine and might cause more adverse effects.<sup>4</sup> Furthermore, the rising cost of liothyronine could adversely affect its availability for patients with thyroid cancer undergoing radioactive iodine treatment. Our findings support the need for urgent measures to reduce the cost of liothyronine to the NHS. Alternatively, if adequately powered, future randomised controlled trials strengthen the evidence base for liothyronine therapy, a better estimate

of the relative costs and benefits could be established.

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See Online for appendix