BJOG: An International Journal of Obstetrics & Gynaecology

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BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE OPEN ACCESS

Hormone Replacement Therapy Uptake and Discontinuation Trends From 1996-2023: An Observational Study of the Welsh Population

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Received: 17 December 2024 | **Revised:** 4 March 2025 | **Accepted:** 7 May 2025

Funding: Peer-reviewed project funded by The Waterloo Foundation, grant reference 1890/5027; the funder is not involved in any aspect of the work. Additional funding for the same project is provided by Health & Her, with Kate Bache involved in the conception of the ideas and the writing of the manuscript.

Keywords: HRT | HRT adherence | HRT discontinuation | HRT trends | menopausal symptoms | menopause | oestrogen

ABSTRACT

Objective: To analyse prescribing trends for oral and transdermal hormone replacement therapy (HRT) in Wales from 1996 to 2023, including predictors of discontinuation within one year of initiation.

Design: Observational study using the Secure Anonymised Information Linkage (SAIL) databank.

Setting: Primary and secondary care data from Wales, encompassing 86% of the population.

Population: Annual HRT prescription rates from 1996 to 2023 were assessed for all women in Wales. Predictors of HRT discontinuation within one year were assessed in women aged 40–65 ($n = 103\,114$), excluding those with oophorectomy, hysterectomy, or premature menopause.

Methods: HRT prescription rates were calculated per 1000 women per year and stratified by HRT type, age groups and deprivation quintiles. Predictors of discontinuation were assessed using a zero-inflated negative binomial regression.

Main Outcome Measures: Annual HRT prescription rates and predictors of discontinuation, including age, deprivation, time period and HRT type.

Results: From 1996 to 2023, 292 707 women were prescribed oral or transdermal HRT in Wales. Transdermal prescriptions rose exponentially post-2021, whereas oral prescriptions declined post-2002. Discontinuation rates followed a curvilinear trend: increasing at ages 40–43 and mid-50s onwards and decreasing in mid-40s to early 50s. Oral formats were linked to decreased discontinuation, whereas transdermals showed increased discontinuation. Deprivation reduced HRT prescriptions overall. Prescriptions post-2000 predicted increased discontinuation, with highest rates seen post-2021.

Conclusions: Disparities in HRT prescribing patterns reflect GP and patient perceptions of safety. Women in their mid-40s to early 50s, often at a natural menopause stage, adhered better, particularly to oral tablets, suggesting that administration route and symptom relief influence adherence. Socio-economic deprivation remains a barrier to HRT access. Time trends highlight the influence of

Previous Dissemination: Andrews. R., Bache. K., Lacey. A., Kidd. E. J (2024, October 15–17). "Hormone Replacement Therapy Uptake & Discontinuation Trends in Wales: 1996-2023" [Oral presentation]. The Royal College of Obstetricians and Gynaecologists (RCOG) World Congress 2024. Muscat, Oman. Andrews. R., Bache. K., Lacey. A., Kidd. E. J (2024, September 10–14). "Hormone Replacement Therapy Uptake & Discontinuation Trends in Wales: 1996-2023" [Poster presentation]. The Menopause Society Annual Meeting: Humanising Artificial Intelligence to Improve Midlife Women's Health. Chicago, Illinois, USA.

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widely publicised studies and media on uptake, albeit adherence has continually declined since 2001. Additional research is needed to tackle socio-economic inequalities and assess strategies for achieving cost-effective and efficient HRT prescribing practices.

1 | Introduction

In recent years, public awareness of menopause has increased significantly [1]. In the United Kingdom (UK), this heightened interest has largely been attributed to high-profile figures and social media influencers raising awareness, as well as the publication of the first NICE guidance on menopause in 2015 [2]. Moreover, a number of documentaries have been released which have educated the public on the challenges women could face during menopause, starting with Mariella Frostrup's documentary, "The Truth about Menopause", in 2018. More recently, UK television presenter Davina McCall has further elevated awareness with her documentaries on menopause, released in 2021 and 2022. These documentaries were viewed by over five million people and led to a 35% increase in hormone replacement therapy (HRT) prescriptions in England [3]. This notable rise in HRT usage has become widely known as "The Davina Effect" [3].

HRT has experienced a turbulent history in the UK. In 2002, following the publication of the findings from the Million Women Study (MWS) [4] and the Women's Health Initiative (WHI) [5], HRT prescriptions dropped sharply. These studies linked HRT to an increased risk of breast cancer and deep vein thrombosis, causing widespread concern. Although subsequent studies suggested that these risks were overstated [6, 7], prescription rates remained low for many years [3].

Davina McCall's documentaries have significantly boosted the prescribing of transdermal HRT in England, particularly because of the growing awareness that transdermal HRT is considered safer than oral formulations [3]. However, it remains unclear how these increased prescriptions have impacted adherence rates, especially as past research indicates lower adherence to transdermal HRT compared to oral formulations [8]. Moreover, the UK has been impacted by HRT shortages in recent years, exacerbated by Brexit and the "Davina Effect" [9] and these shortages could also be affecting women's adherence to HRT.

Evidence from the USA suggests high discontinuation rates of HRT, with 35%–40% of women stopping treatment after their first prescription [10]. Common reasons for discontinuation include lack of symptom improvement, side effects such as unscheduled bleeding, and doctor's advice due to ongoing safety concerns [11]. There is also a growing trend of younger women being prescribed HRT [12]. However, findings from the Study of Women's Health Across the Nation (SWAN) based in the USA suggest that ~45% of perimenopausal women will experience periodic surges in oestradiol levels [13]. These surges result in higher levels of oestradiol than recorded during pre-menopause, which could cause symptoms that can be exacerbated by HRT, leading to side effects [13].

Although there have been recent assessments of HRT prescribing trends in England [14], there has been no evaluation of these trends in Wales. As the most deprived country in Britain [15], Wales presents a unique case, where it remains unclear how levels of deprivation might influence HRT prescribing and adherence. Additionally, Wales operates a devolved healthcare system with prescribing practices that differ from those in England. Since 2007, Welsh patients have had access to free prescriptions for most NHS drugs, including HRT [16]. Given the lack of data from Wales, it is essential to investigate this population to understand HRT usage patterns.

1.1 | Objectives

This study aims to examine annual trends in HRT prescribing in Wales and identify predictors of discontinuation for both transdermal and oral HRT within one year of initiation. We sought to evaluate HRT prescribing rates across Wales from 1996 to 2023 and identify key indicators for discontinuation. This would allow us to account for contextual factors in HRT prescribing and adherence in subsequent work, ensuring that the role of HRT in managing menopausal symptoms and future health outcomes is considered fully.

The key research questions are:

1. What are the trends in prescribing transdermal and oral HRT preparations in Wales from 1996 to 2023?
2. What factors influence adherence to transdermal and oral HRT within one year of initiation?

2 | Methods

2.1 | Data Source

Prescribing data from 1 January 1996 to 31 December 2023 obtained from the Secure Anonymised Information Linkage (SAIL) databank [17, 18] were examined using a retrospective, cross-sectional study design. The study was approved by the Information Governance Review Panel in SAIL (SAIL identification no. 1448) and is part of a peer-reviewed project funded by The Waterloo Foundation, grant reference: 1890/5027.

The SAIL databank was established in 2007, but the available datasets are backdated, even as new data sources come online. Unique Anonymous Linkage Fields (ALFs) are allocated to person-based records within the SAIL datasets, allowing data linkage to provide a record of all healthcare interactions for the individual (ALF_PE). Consequently, the SAIL datasets allow longitudinal research in large population groups across Wales. The SAIL databank contains anonymous patient records, representing approximately 86% of the total population of Wales as of the data extract date in August 2024. The remaining 14% include individuals who live along the Welsh border who are registered with GPs governed under NHS England and those registered at practices which do not supply data to SAIL [19]. However, the primary care population covered within SAIL is representative of the Welsh population as a whole [19].

2.2 | Cohort

2.2.1 | Prescription Trends

Women ($n = 292\,707$) prescribed oral or transdermal menopausal HRT medications between 1996 and 2023 were identified from the SAIL datasets by individual Read codes for each medicine (see Table S1 for Read codes used to identify HRT prescriptions). Read codes, a thesaurus of clinical terms, are currently used for recording all interactions, diagnoses and interventions within primary care in Wales, with a reliance on individual practitioners to input codes regarding investigations and diagnoses. However, prescriptions are automatically coded at input and, consequently, this is a reliable method of data identification and has been validated by its use in other studies [19–22]. Read codes for prescribable HRT preparations were taken from the Clinical Terminology Browser available from the NHS Information Authority and accessed via the SAIL gateway.

Prescription trends for HRT preparations, including transdermal, oral and local preparations, were identified within the Primary Care General Practice database using Read codes Version 2 for the individual product (see Table S1).

All HRT prescriptions were linked to individual patient demographic data using unique identifiers: ALF PEs. SAIL uses a split-file anonymisation method to maintain confidentiality. Individuals within each routinely collected dataset are assigned a unique identifier (Anonymised Linking Field [ALF]). The ALF is generated by NHS Wales Information Service, a trusted third party, using the Matching Algorithm for Consistent Results in Anonymised Linkage. Data relating to male patients were removed, and only patients who initiated HRT for the first time during the study period (1996–2023) were included.

2.2.2 | Predictors of Discontinuation Within One Year of Initiation

In this study, 'Discontinuation within One Year of Initiation' was defined as having been prescribed transdermal or oral HRT for fewer than 365 days, based on the time elapsed between the first and last recorded prescription dates. Women were classified as discontinued if they had no further HRT prescriptions within the study window (1996–2023). This approach was chosen because HRT is typically continued for at least a year to effectively manage symptoms. To ensure sufficient follow-up time, we restricted the analysis to women who initiated HRT between 1996 and 2021.

This analysis was conducted among women ($n = 103\,114$) who were deemed to be spontaneously transitioning through menopause, that is, had not undergone a hysterectomy or bilateral oophorectomy, or been diagnosed with primary or secondary ovarian failure. We adopted this approach because women with these characteristics often require HRT for osteoporosis prevention or are eligible for oestrogen-only HRT, meaning their reasons and patterns for discontinuation may differ significantly from those experiencing spontaneous menopause. Occurrence of surgeries which could induce menopause was identified from the secondary care operations database and the primary and secondary care databases. Diagnoses of primary and secondary ovarian failure were determined through primary care data. Primary ovarian failure is diagnosed when a woman reaches menopause before 40; therefore, we focused this sub-analysis on women aged 40–65. Table S1 includes the codes used to identify surgical or premature menopause.

In this analysis users' discontinuation status was censored if they moved out of Wales within one year of being prescribed HRT. Moving out of Wales was determined using the Welsh Demographic Service Dataset (WDSD) in SAIL. Discontinuation was also censored if users died within one year of being prescribed HRT, as identified using the Office for National Statistics (ONS) Death Registration Table in SAIL [23].

2.3 | Patient Involvement

Conceptualisation of this study was presented during a SAIL Consumer Panel Meeting hosted by Swansea University's Population Data Science division. Consumer panellists were from diverse academic and professional backgrounds. Panellists, some of whom were women who had been prescribed HRT, provided advice and recommendations for developing the research question, choosing outcome measures and study design. The authors encouraged feedback and discussion from individuals affected by menopause to develop meaningful outcomes from the study and to develop further research.

2.4 | HRT Utilisation

The number of prescriptions per year, stratified by HRT type (oestrogen gels, oestrogen patches, oestrogen tablets, combined patches, combined tablets), was calculated as repeat cross-sectional estimates for each year from 1996 to 2023. Prescription rates were calculated per 1000 people in the annual population within the WDSD dataset [24], and further stratified by age group (< 40, 40–44, 45–49, 50–54, 55–59, 60+) and Townsend deprivation quintile, following the methods of Davies et al. [20].

Code lists for prescriptions of HRT medicines were based on British National Formulary (BNF) chapter 6.4.1, except for oestrogen-receptor modulators. Types of HRT were based on Anatomical Therapeutic Chemical (ATC) classification: oestrogens and combination regimens of oestrogen and progestin (OP) in sequential preparations or continuous combinations. Separately, prescriptions for testosterone hormone therapy were retrieved. Routes of administration were grouped as the following: oral route including tablets and capsules and transdermal formulations (patches and gels). All oral and transdermal formats were included, but progesterone-only preparations, such as Utrogestan and levonorgestrel-releasing intrauterine devices, were excluded so as not to 'double count' HRT prescriptions or count progestins used for contraceptive purposes. Intranasal and implant preparations were initially included separately, however, prescribing rates for these formulations were too low to gather meaningful outcomes therefore these instances were excluded. Local oestrogens (vaginal creams and pessaries) were explored in the discontinuation analysis to control for the effects of being prescribed this formulation on HRT adherence. Testosterone was also included in the discontinuation analysis for the same reason.

Local oestrogens and testosterone were not compared alongside transdermal and oral HRT in the trends analysis because, while these medications are classed as HRT, they are prescribed for specific separate symptoms (urogenital and low sexual desire, respectively) and are therefore not comparable to transdermal and oral formats which are both indicated for a wider range of vasomotor symptoms (VMS). However, the use of transdermal testosterone and local oestrogen were included in the discontinuation analysis as independent predictors. For all Read codes used in this analysis see Table S1.

2.4.1 | Deprivation

The Townsend index [24] was used to determine relative deprivation of areas within Wales. The index is constructed from an individual's home postcode and the following four census variables, each of which must be divided by the appropriate count of households or persons to obtain a percentage score.

- Households without a car
- Overcrowded households
- Households not owner-occupied
- Persons unemployed

The unemployment and overcrowding percentages (+1) are then subjected to a log transformation to normalise the raw values, which tend to be highly skewed. All four variables are then standardised using a *Z*-score. These four standardised scores are then summed to obtain a single value which is the Townsend deprivation index. Higher values indicate areas with high material deprivation, whereas lower values indicate relative affluence. Therefore, a Townsend quintile of 1 represents the least deprived areas, whereas 5 represents the most deprived areas. A Townsend deprivation quintile was identified per ALF_PE using the Welsh WDSD table.

2.4.2 | Age at Initiation

In SAIL, to protect patients' anonymity, week of birth is used as a proxy for their birthdate. Week of birth is defined as the Monday of the week of their birthdate. We extracted each patient's week of birth from the primary care table and used the first date they were prescribed HRT to calculate their age at initiation.

The association between age and VMS is curvilinear: frequent and bothersome VMS are unlikely during pre-menopause, will usually first emerge during perimenopause and peak in severity around the time of the final menstrual period before abating in the postmenopausal years [25]. Therefore, we opted to evaluate discontinuation in relation to age at initiation in a non-linear way by using the following age brackets: 40–41, 42–43, 44–45, 46–47, 48–49, 50–51, 52–53, 54–55, 56–57, 58–59, 60–65.

2.4.3 | Time Period

To evaluate how historical events relating to HRT influenced discontinuation within one year, we identified time periods where HRT prescription rates saw notable national changes by assessing the literature and visually inspecting annual prescription rates on a line graph to observe notable changes.

This Process Resulted in the Identification of 7 Distinct Periods:

- 1996–1998: Before publication of MWS/WHI studies
- 1999–2001: Immediately before publication of MWS/WHI studies
- 2001–2005: Immediately after publication of MWS/WHI studies
- 2006–2010: Early flat period
- 2011–2015: Late flat period
- 2016–2019: Gradual incline
- 2019–2020: COVID-19
- 2021–2023: Davina effect

We decided to evaluate early and late "flat periods" (i.e., periods where HRT prescribing rates were relatively flat following publication of the MWS/WHI studies) separately to explore whether any temporal differences existed in relation to discontinuation during these periods, as prior evidence has shown that discontinuation rates were higher in the immediate years following publication of the MWS/WHI studies than in the latter years [26]. In 2016 up until 2019, there was a gradual incline in prescribing rates; this is likely due to the publication of the first NICE guidance on Menopause in 2015 [27], as suggested by prior UK trends analyses [12], which likely helped renew GPs' confidence in prescribing HRT.

2.4.4 | Covariates

We controlled for the impact of cancer diagnoses as a binary (Yes/No) variable identifying those who had been diagnosed with cancer one year before or after HRT prescription dates (thus excluding diagnoses which occurred after the date of HRT discontinuation), as oestrogen-dependent cancer diagnoses are a key contraindication for HRT use [28], and evidence suggests that GPs' are also reluctant to prescribe, or continue to prescribe, HRT in those with non-oestrogen-dependent cancers [29]. We also controlled for the use of local oestrogen (e.g., vaginal creams or pessaries), and the use of transdermal testosterone as binary (Yes/No) variables. This is because the use of these medications can supplement the efficacy of transdermal and oral HRT regimens. See Table S1 for all Read codes.

2.5 | Data Analysis

2.5.1 | Annual Prescription Rates per 1000

Data were extracted from the study tables within SAIL using the Eclipse software. The extracted data was then visualised using ggplot2 [30] via RStudio version 4.3.3 [31]. Trend rates were calculated as the number of HRT prescriptions per 1000 people registered with a Welsh GP per year, stratified by Townsend

deprivation quintile (1 = Least deprived, 5 = Most deprived), HRT route of administration (oestrogen gels, oestrogen patches, oestrogen tablets, combined patches, combined tablets) and age bracket (< 40, 40–44, 45–49, 50–54, 55–59, 60+). This analysis included all women prescribed HRT between 1996 and 2023, aged 18 +.

2.5.2 | Predictors of Discontinuation Within 1 Year

A zero-inflated negative binomial regression was used to evaluate predictors of discontinuing HRT within one year of initiation using R package 'pscl' [32]. This type of regression was employed to account for overdispersion and excess zeros [33]. We opted not to conduct a Cox model as our main analysis because HRT continuation rates are strongly impacted by cultural and contextual factors (e.g., policy and media-driven shifts in HRT prescribing practices). These factors mean that HRT continuation is not proportional over time, violating the assumptions of a Cox model. Furthermore, the exact time of discontinuation could not be ascertained from the prescription dates. In these cases a negative binomial model is recommended [34].

To compute the negative binomial regression we aggregated the data to assess counts of discontinuation events in different groups. We counted instances of the number of patients who discontinued HRT within one year according to HRT type (oestrogen gels, oestrogen-only patches, combined patches, combined tablets, oestrogen-only tablets), deprivation quintile, age bracket, year, cancer diagnosis within a year of initiation of HRT (Y/N), time period, local oestrogen use (Y/N) and testosterone gel use (Y/N). Year was used as the predictor for the zero-inflation part of the model as it was determined that Year was the variable responsible for excess zeros due to temporal lulls in HRT prescribing.

Descriptive statistics and regression results were tabulated using R package gtsummary [35], and a forest plot for the regression was generated using ggplot2 [30].

As the negative binomial regression demonstrated a curvilinear effect of age, this effect was modelled using a Cox proportional hazards regression to assess whether this effect remained using a time-to-event model and age as a continuous variable. This regression included all predictor variables and a spline for age using the SurvivoR package [36]. Using the termplot function in the survival package [37], a plot was generated to visualise the curvilinear effect of age on discontinuation of transdermal and oral HRT.

3 | Results

3.1 | Descriptive Statistics

There were 292 707 women who had been prescribed oral or transdermal HRT in Wales between 1996 and 2023 (Table 1). Table 1 shows the differences between women in the sub-sample ($N = 103\,114$) alongside those not included in the sub-sample ($N = 189\,593$). Women in the discontinuation sub-sample had a shorter duration of use, and there were fewer

TABLE 1 | Characteristics of women in the sub-sample versus not in the sub-sample.

Cohort, $N = 292\,707$		
Characteristic	**In sub-sample, $N = 103\,114$[a]**	**Not in sub-sample, $N = 189\,593$[a]**
Age at first use	51 (5)	51 (9)
Duration of use (days)	597 (82, 1655)	1161 (277, 2660)
Time period		
1996–1998: Before MWS/WHI	17 372 (17%)	61 871 (33%)
1999–2000: Shortly before MWS/WHI	11 132 (11%)	16 053 (8.5%)
2001–2005: Immediately after MWS/WHI	21 795 (21%)	28 157 (15%)
2006–2010: Early flat period	11 277 (11%)	12 344 (6.5%)
2011–2015: Late flat period	11 227 (11%)	11 553 (6.1%)
2016–2018: Gradual incline	9352 (9.1%)	9465 (5.0%)
2019–2020: COVID-19	6228 (6.0%)	7727 (4.1%)
2021–2023: Davina effect	14 731 (14%)	42 423 (22%)
First HRT prescription		
Combined patches	15 538 (15%)	21 234 (11%)
Combined tablets	64 210 (62%)	53 770 (28%)
Oestrogen gels	5755 (5.6%)	18 604 (9.8%)
Oestrogen patches	7004 (6.8%)	40 556 (21%)
Oestrogen tablets	10 607 (10%)	55 429 (29%)
Deprivation quintile		
1. Least deprived	15 329 (15%)	30 014 (16%)
2	19 521 (19%)	37 981 (20%)
3	25 724 (25%)	47 082 (25%)
4	19 805 (19%)	34 695 (18%)
5. Most deprived	22 735 (22%)	39 821 (21%)
Used local oestrogen	11 120 (11%)	37 615 (20%)
Used testosterone	463 (0.4%)	2170 (1.1%)
Diagnosed with cancer[b]	1415 (1.4%)	3576 (1.9%)
Died[b]	274 (0.3%)	376 (0.2%)
Migrated from Wales[b]	1442 (1.4%)	1823 (1.0%)

Abbreviations: HRT, hormone replacement therapy; MWS, Million Women Study; WHI, Women's Health Initiative.
[a]Mean (SD); Median (IQR); *n* (%).
[b]Within a year of being prescribed HRT.

women who had been prescribed HRT between 1996 and 1998 in the sub-sample, but more women who were prescribed HRT between 2001 and 2005, in both flat periods, the gradual incline and during COVID-19. Fewer women in the sub-sample had been prescribed HRT during the "Davina Effect" years because only women first prescribed HRT between 1996 and 2021 were included in the sub-sample, so we could accurately ascertain whether they were still being prescribed HRT a year or more later. The use of combined tablets and combined patches was much higher in the discontinuation sub-sample, whereas the use of oestrogen-only products was lower. Fewer women in the sub-sample had used local oestrogen alongside their transdermal or oral HRT, and hardly any had used transdermal testosterone. Slightly fewer women in the sub-sample had been diagnosed with cancer within a year of HRT treatment. There was a similar distribution of women in the deprivation quintiles in both groups.

3.2 | HRT Prescription Rates per Year by Administration Route

As shown in Figure 1, the rates of HRT prescribing for combined and oestrogen-only tablets were at high levels during the mid-1990's up until 2001. Oestrogen patches were the third most commonly prescribed type during this period, followed by combined patches. The use of oestrogen gels was very low, probably due to limited availability of this format [38].

From 2002 onwards, all HRT types, bar oestrogen gels, saw large declines in prescription rates, with exponential decreases year-on-year until 2005. From 2006 until 2010, HRT prescribing rates were flat for all types, except for tablets which showed gradual declines in use. From 2011 to 2015, oestrogen patches, oestrogen gels and combined patches had continued flat prescribing rates, while oestrogen tablets declined, but combined tablets showed a gradual increase. From 2016 to 2019, all HRT types showed gradual increases in use, except for oestrogen tablets which continued to decline. From 2019 to 2020, several HRT types saw a slight decline in use, likely due to the COVID-19 pandemic, except for oestrogen patches and oestrogen gels which saw an increase in use. From 2021 to 2022, the use of all transdermal HRT formulations increased exponentially, whereas oestrogen-only and combined tablets declined. Rates for transdermal prescriptions remained high in 2023.

3.3 | HRT Prescription Rates per Year by Age Bracket

As shown in Figure S1, prescription rates per year for all forms of HRT were relatively stable until 2002 but then declined sharply in all age groups until 2005. Between 2006 and 2014, prescribing rates were relatively flat in all age brackets. Then, from 2015 until 2019, most age brackets saw year-on-year increases in prescribing rates, with women between 50 and 54 seeing the greatest increases, but prescribing in women under 40 and aged 40–44 remained flat. From 2019 to 2020, there was a decrease in prescribing rates for all age brackets. From 2020 to 2022, all age brackets saw exponential increases in prescribing year-on-year, with women aged 45–54 having the largest increases, followed by women aged 40–44. In 2023, prescribing rates were lower than 2022 for women aged 45–59, although remaining high compared to pre-2020 rates, but continued to rise for women under 40 and those aged 40–44 and over 60.

3.4 | HRT Prescription Rates per Year by Townsend Deprivation Quintile

As shown in Figure S2, during the 1990's quintiles 1, 2 and 3 had similar levels of prescribing rates with 1 and 2 having the highest rates. The most deprived quintile 5 had the lowest prescribing rates across all years, followed by quintile 4. Prescribing rates declined in all deprivation quintiles from 2002 to 2005. Between 2006 and 2015, prescribing rates remained relatively flat across all quintiles except for quintile 1 where prescribing gradually

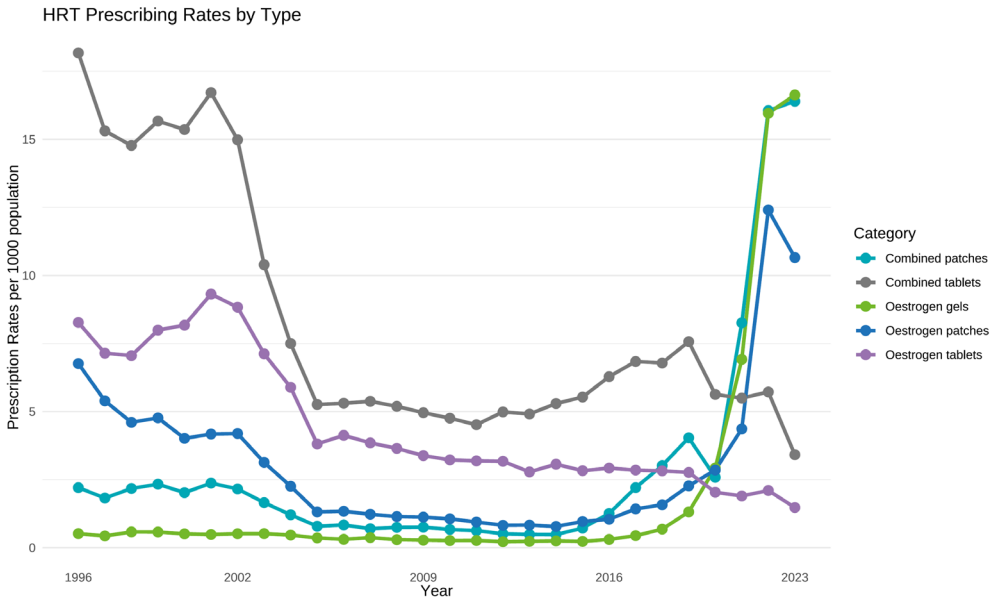

FIGURE 1 | HRT prescription rates per year by administration route.

increased from 2006 onwards. From 2016 to 2019 prescribing rates increased across all quintiles, but declined in 2020, due to the COVID-19 pandemic. Then, from 2020 to 2022 all quintiles saw exponential increases in prescribing, with rates remaining high in 2023.

3.5 | Adherence to HRT

Of the 103 114 women included in the sub-sample, 40% ($N = 41\,736$) discontinued HRT within a year of initiation and 20% ($N = 20\,462$) received one prescription only. The average number of prescriptions received before discontinuation within a year was 3.7 (SD = 2.9). The median time to discontinuation within a year was 162 days (IQR = 43, 265).

The regression results for factors which could predict discontinuation of HRT within one year of initiation highlighted age at initiation of prescribing, HRT type, the year of initiation and deprivation as having the greatest effects on whether a woman continued to take HRT once prescribed (Table 2). A curvilinear pattern for age at initiation was observed for discontinuation within 1 year with an age spline plot (Figure S3). Discontinuation rates were increased among women aged 43 and under, decreased in those from 44 to 51 and then increased again from age 53 onwards, as shown on the spline plot (Figure S3). Both combined and oestrogen-only tablets were significantly more likely to be adhered to past 1 year than all transdermal formats (oestrogen gels, oestrogen and combined patches) (Table 2). The 1990s had the lowest discontinuation rates. Adherence fell for all women post-MWS and WHI publication and was also reduced by the COVID-19 pandemic but not above the preceding rates. The "Davina Effect" on prescribing (2021–2023) was associated with the highest discontinuation rates (Table 2). The second poorest quintile (Quintile 4) had significantly higher discontinuation rates than the wealthiest quintile (Quintile 1); however, all other quintiles were not significantly associated with variances in discontinuation rates (Table 2). Cancer diagnosed within one year of prescription was associated with the largest increase in discontinuation in any group (Table 2). Local oestrogen or testosterone gels were also both associated with increased discontinuation rates (Table 2).

TABLE 2 | Predictors of discontinuation of HRT within one year.

Characteristic	IRR	95% CI	*p*
Age group			
40–41	1.00	—	
42–43	0.98	0.91, 1.05	0.5
44–45	0.90	0.84, 0.96	0.001
46–47	0.89	0.83, 0.95	< 0.001
48–49	0.82	0.77, 0.88	< 0.001
50–51	0.89	0.84, 0.95	< 0.001
52–53	0.93	0.87, 0.99	0.029
54–55	1.00	0.93, 1.07	> 0.9
56–57	1.06	0.98, 1.14	0.13
58–59	1.20	1.10, 1.30	< 0.001
60+	1.34	1.23, 1.47	< 0.001
HRT type			
Combined patches	1.00	—	
Combined tablets	0.52	0.50, 0.54	< 0.001
Oestrogen gels	1.15	1.09, 1.21	< 0.001
Oestrogen patches	1.17	1.12, 1.22	< 0.001
Oestrogen tablets	0.88	0.85, 0.92	< 0.001
Time period			
1996–1998: Before MWS/WHI	1.00	—	
1999–2000: Shortly before MWS/WHI	0.81	0.75, 0.87	< 0.001
2001–2005: Immediately after MWS/WHI	1.13	1.07, 1.21	< 0.001
2006–2010: Early flat period	1.23	1.15, 1.31	< 0.001
2011–2015: Late flat period	1.20	1.12, 1.28	< 0.001
2016–2018: Gradual incline	1.13	1.05, 1.21	< 0.001
2019–2020: COVID-19	1.14	1.06, 1.22	< 0.001
2021–2023: Davina effect	1.59	1.49, 1.69	< 0.001
Townsend quintile			
1. Least deprived	1.00	—	
2	1.01	0.97, 1.06	0.6
3	1.04	0.99, 1.08	0.089
4	1.07	1.03, 1.12	0.002

(Continues)

4 | Discussion

4.1 | Main Findings

This study highlights key trends in HRT uptake and adherence among women in Wales, with age at initiation and formulation playing a particularly important role in adherence. Women in their mid-40s to early 50s were more likely to adhere to HRT beyond one year. Younger women showed much lower adherence rates, despite meeting criteria for early menopause. There was a significant shift from oral to transdermal HRT prescribing over time, probably spurred by both increased awareness, notably through the "Davina Effect," and changing perceptions of safety. However, adherence to transdermal HRT remained poorer than for oral forms. The study also found that socio-economic status

TABLE 2 | (Continued)

Characteristic	IRR	95% CI	*p*
5. Most deprived	1.03	0.98, 1.07	0.2
Used testosterone	1.17	1.07, 1.27	< 0.001
Used local oestrogen	1.25	1.21, 1.29	< 0.001
Cancer diagnosis[a]	13.6	12.9, 14.4	< 0.001

Abbreviations: CI, confidence interval; HRT, hormone replacement therapy; IRR, incidence rate ratio; MWS, Million Women Study; WHI, Women's Health Initiative.
[a]Within a year of being prescribed HRT.

influenced HRT uptake, with lower prescribing rates observed in more deprived areas. Interestingly, while deprivation appeared to impact access to prescriptions, it had less influence on discontinuation. This study provides new insights into how age, socio-economic factors and public awareness campaigns impact HRT usage and subsequent adherence.

4.2 | Interpretation

Annual trends in HRT prescribing in Wales were similar to those in England. A study by NHS England found that HRT prescribing increased by 47% from 2021/2022 to 2022/2023, indicating that the "Davina Effect" also influenced the English population [14]. These findings differ from a recent study [39] conducted in the USA which found HRT use among postmenopausal US women has declined significantly since 1999. This difference suggests that the media plays a significant role in HRT prescribing, shown via the publicisation of the WHI and MWS results and the Davina Effect suggesting that, when educated, more women are willing to use HRT. Similar to our study, more younger US women are being prescribed HRT in recent years than in the 1990's and 2000's, reflecting emerging data suggesting that HRT is safer when used at an earlier age [39].

In our sub-sample of spontaneously menopausal women, 40% discontinued HRT within a year of initiation. This differs from a US study by Ettinger et al. [10], who found that 50% of women enrolled in a health plan with oestrogen prescription costs ranging from zero to $21 for a 100-day supply discontinued HRT within a year. However, Hill et al. [40] also reported that 40% of women who were enrolled in a prepaid health plan, where prescription costs were covered, discontinued within a year. This suggests that cost-related factors may have contributed to the higher discontinuation rate observed by Ettinger et al. [10], as HRT prescriptions have been free in Wales since 2007.

Women in their mid-40s to early 50s were the most likely to adhere to HRT beyond one year, suggesting this age range is optimal for HRT adherence. Surprisingly, younger women (aged 40–43) tended to have poorer adherence. This is despite women under the age of 45 meeting the criteria for early menopause and therefore having a greater need for bone protection through HRT to prevent osteoporosis [41] than older age groups [42]. A potential reason for this finding could be the higher oestradiol levels found in younger women, which may cause HRT side effects such as heavy bleeding, breast tenderness and mood disturbances [13] thus leading to discontinuation. Furthermore, menopausal symptoms have been found to peak as women approach their final menstrual period [43]. UK women are aged 51 on average at their final menstrual period, and adherence rates were highest around this age in this study. Therefore, these results may reflect that younger women have less severe menopausal symptoms or may have initiated HRT before their menopausal symptoms have fully emerged. Additionally, younger women may have concerns about cancer risks that outweigh their symptom severity, as there is still a significant lack of understanding about the relative risk of HRT for cancer development [29].

The study also revealed significant disparities in prescribing patterns for different types of HRT. While oral prescriptions declined over the study period, there was a rapid rise in transdermal prescriptions, probably reflecting both GP and patient perceptions of safety and the "Davina Effect" which increased awareness and prescribing of these formulations [3]. However, adherence to transdermal HRT was generally poorer than to oral HRT, consistent with earlier research [8, 26]. This could be explained by the inconvenience of applying patches or gels or inadequate symptom control due to poor absorbency [44].

The use of local oestrogen and transdermal testosterone was also associated with increased discontinuation. This is possibly related to the age at which women were using these forms, as vaginal and sexual symptoms arise later in the menopause transition and are therefore more likely to affect older women [45]. This theory is consistent with our data showing that, from their late 50's onwards, women were more likely to discontinue transdermal or oral HRT than younger age groups. These results for older women being more likely to have discontinued HRT than younger age groups were expected given that NICE recommendations [27] stipulate that the risks of HRT can outweigh the benefits for older women, especially after the age of 60.

We found that the timing of HRT initiation plays a role in adherence, with women prescribed HRT from 1996 to 2000 being more likely to continue past one year than those prescribed in later time periods. Prescriptions after 2001 were associated with increased discontinuation due to publication and subsequent publicity in the UK of the MWS [4] and WHI [5] findings, which indicated that HRT was associated with increased cancer and cardiovascular risks. Although these risks were subsequently found to have been exaggerated [46], the influence of these studies still affects HRT prescribing [7]. Notably, prescriptions related to the "Davina Effect" (2021–2023) were associated with the highest rates of discontinuation. This could be due to increased awareness of menopause and HRT during this time, as the trends analysis demonstrated a huge increase in the number of women requesting HRT from their GPs, thus resulting in larger rates of discontinuation. A contributing factor to this outcome could also be related to shortages of products exacerbated by Brexit and the "Davina Effect". From 2018 onwards, HRT shortages particularly impacted oestrogen gels, oestrogen patches and combined patches [9] and these shortages could thus have contributed to the increased rates of discontinuation of transdermal formulations compared to oral formats. However, controlling for time should have attenuated this issue, and a

sub-analysis (data not shown) exploring date ranges up to 2020 (prior to the "Davina Effect" and subsequent supply issues) still demonstrated that transdermal formulations had higher rates of discontinuation than oral forms. This suggests alternate mechanisms for this association that require further investigation.

Deprivation had a clear relationship with HRT uptake, with the poorest quintiles having the lowest prescribing rates, and the wealthiest quintiles having the highest prescribing rates. This result is consistent with a study in England which demonstrated that the overall prescribing rate of HRT was 29% lower in GP practices from the most deprived quintile compared with the most affluent [47]. Studies which have evaluated health care access and Townsend deprivation quintiles in the UK in relation to other conditions have also found inequalities. For example, an analysis of the IQVIA Medical Research Data dataset demonstrated that people with type 1 or type 2 diabetes and chronic kidney disease from the most deprived areas were less likely to have blood pressure measurements or be prescribed renin–angiotensin–aldosterone system inhibitors than patients from the least deprived areas [48]. These findings support other data showing that more deprived areas in Wales have poorer access to healthcare than wealthier areas [49] and GP practices in poorer areas have significantly less funding per patient [50]. Regarding discontinuation, the relationship with deprivation was much less clear. Only quintile 4, the second poorest quintile, was associated with significantly increased discontinuation rates compared to quintile 1. This result could be due to variances in healthcare access across GP practices; those women who could access a GP to prescribe them HRT were able to continue doing so while those with no access to their GP would never be able to get a prescription so could not have higher rates of discontinuation. Alternatively, deprivation may not have strongly influenced discontinuation rates after controlling for the other factors. This has been evidenced by earlier research utilising the SAIL databank examining socio-economic inequality in the persistence of coronary heart disease medication [51].

4.3 | Strengths & Limitations

One of the key strengths of this study is its long-term scope, analysing HRT prescribing trends from 1996 to 2023. Many previous studies based in the UK focused on shorter time frames, such as 1991–1995 [52] or 2010–2021 [12] or limited their sample to women aged 50 and older [12]. By offering a comprehensive, longitudinal view, this study contextualises prescribing trends against significant historical events in menopause care, including the MWS, WHI, COVID-19 and the "Davina Effect". Furthermore, this is the first study to focus specifically on the Welsh population, providing unique insights into HRT prescribing patterns and adherence in a country with a devolved healthcare system and distinct levels of deprivation. Past evidence has validated the sensitivity and accuracy of the SAIL databank for evaluating prescription data [19]; and the inclusion of socio-economic factors, such as deprivation, and their relation to HRT uptake adds further depth to the analysis.

However, the study also has limitations. Firstly, the data is sourced from NHS GP practices within the SAIL Databank, which may limit generalisability beyond Wales or public healthcare settings. Notably, this study does not account for privately prescribed HRT adherence rates. Testosterone, in particular, is available in more formats (e.g., Androfeme) through private channels than through the NHS [53], which may explain the low rates of testosterone use observed in this study. However, given that only 0.006% of the Welsh population had private health insurance in 2023, the exclusion of private medical data is unlikely to have significantly impacted these findings.

Secondly, the findings of the sub-study apply to women who have undergone a spontaneous menopause and therefore cannot be used to determine HRT continuation rates among women with premature menopause, or who have undergone a bilateral oophorectomy or hysterectomy. The descriptive data demonstrated key differences between women included and excluded in the discontinuation sub-study. Women in the discontinuation sub-sample had a shorter duration of use. This is probably due to the exclusion of women who had undergone surgical or early onset menopause, which would lead to longer usage durations of HRT due to the recommendation to continue using HRT until the national average age at menopause (51 years) to reduce risks of osteoporosis [41]. The use of combined tablets and combined patches was much higher in the discontinuation sub-sample while the use of oestrogen-only products was lower. This is expected because women were excluded from the sub-sample if they had undergone a hysterectomy. Women without a womb can take oestrogen-only HRT; however, women with a womb must take combined HRT as progestogen is protective against endometrial cancer, which can occur with oestrogen-only formats when the womb is still intact [54]. These differences suggest that continuation rates may be higher among women with additional medical indications for HRT (aside from symptom control), such as bone protection. Moreover, oestrogen-only formulations may be tolerated better than combined formats which do not require supplementary progestogen; this should be explored in future research.

Thirdly, while the sample size is large and representative of the Welsh population, the study could not assess the reasons for HRT discontinuation, which could provide critical insights into the barriers to adherence. The most influential reason for HRT uptake and adherence is menopausal symptom control, which we could not capture in the present study. While menopausal symptoms can and are recorded in primary care data, some GPs are more likely to record them than others, leaving vast disparities in menopausal symptom recording across practices [55]. The SAIL databank is not designed to adequately capture the reasons for these variances [55]. Thus, any assessment of menopausal symptoms in relation to HRT use using SAIL would be highly flawed and would state more about help-seeking behaviour, service capacity and practice priorities than HRT adherence [55]. For this reason, we opted not to include menopausal symptom records in our analysis. Therefore, future research is required to explore the reasons for poor adherence to HRT, addressing socio-economic disparities in HRT access, and developing strategies to improve both adherence and access, especially among more deprived groups.

5 | Conclusion

This study underscores the complexity of HRT prescribing trends, adherence and the impact of public awareness in Wales.

Women in their mid-40s to early 50s exhibited the highest rates of long-term adherence, suggesting that this age group may be optimal for HRT intervention. The study highlights the dramatic shift from oral to transdermal HRT formulations, influenced in part by the "Davina Effect" and evolving perceptions of safety. However, transdermal formats saw higher rates of discontinuation, reflecting ongoing challenges related to application convenience and absorption efficacy.

Deprivation played a significant role in HRT prescribing, with women from the poorest quintiles having the lowest prescribing rates. While access to HRT remains an issue in deprived areas, the relationship between socio-economic status and HRT discontinuation requires further investigation.

Moving forward, future research should explore the causes of discontinuation, focusing on symptom control, socio-economic barriers, side effects and patient perceptions of HRT risks. The findings from this study will provide a foundation for future work in improving HRT prescribing practices and adherence, particularly as public awareness of menopause and its treatments continues to grow.

Author Contributions

Robin Andrews conceived the study, developed and conducted the analysis and wrote the first draft of the manuscript. Arron Lacey conceived the study and advised on the methods and data analysis, and reviewed and revised the manuscript. Kate Bache conceived the study and advised on the methods and data analysis, and reviewed and revised the manuscript. Emma J. Kidd conceived the study and advised on the methods and data analysis, and reviewed and revised the manuscript. All authors saw and approved the final version, and no other person made a substantial contribution to the paper.

Ethics Statement

Prescribing data from 1 January 1996 to 31 December 2023 obtained from the Secure Anonymised Information Linkage (SAIL) databank were examined using a retrospective, cross-sectional study design. The study was approved by the Information Governance Review Panel in SAIL (SAIL identification no. 1448) in May 2023.

Conflicts of Interest

R.A. is employed by Health & Her. A.L. is a consultant for Health & Her. K.B. is the co-founder and CEO of Health & Her.

Data Availability Statement

The routine data used in this study are available in the SAIL Databank at Swansea University, Swansea, Wales, UK. All proposals to use SAIL data are subject to review by an Independent Governance and Review Panel (IGRP). When access has been approved, it is gained through remote access to a trusted research environment (TRE) known as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL: https://www.saildatabank.com/application-process. This study has been approved by the IGRP as project 1448.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.