

# **The mental health associations with vitiligo: a population-based cohort study in the UK [Study protocol]**

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## Background

Vitiligo is an acquired skin disorder characterised by depigmented patches of skin that may appear in a localised or generalised distribution. Vitiligo is estimated to affect 0.5-2% of the global population with an equal incidence between genders, age or racial/ethnic groups [1]. The exact cause of the loss of functioning melanocytes in vitiligo remains unknown but is likely to be resulted from the complex interplay of genetics, oxidative stress, and autoimmunity [2].

Although vitiligo is typically asymptomatic, it may substantially affect the psychological wellbeing of people living with the condition [3]. This could be due to the unpredictable prognosis, the current lack of cure or the perception and emotional burden associated with the visibility of vitiligo. A recent systematic review has shown that people with vitiligo are significantly more likely to suffer from depression and anxiety compared to the healthy controls [4]. However, there is a lack of knowledge of the other types of psychological symptoms/disorders that people with vitiligo experience [5].

Human society places a profound significance on appearance, aesthetics and pigmentation [6]. Vitiligo is visible on all skin types, and is particularly noticeable on dark skin tones because of the strong contrast. Given the visible difference in appearance of affected and unaffected areas of the skin the condition has been construed as being disfiguring. Some studies have suggested in those with darker skin vitiligo is correlated with a worse quality of life (QoL) [7, 8]. However, these studies have small sample sizes and psychiatric comorbidities and psychological wellbeing were not evaluated in the analyses. Further, there are other studies that indicate that people with lighter skin tones may also experience distress [9].

In addition to skin colour, the location of vitiligo lesions may also influence the overall well-being and stigmatisation experience of patients. However, inconsistent findings have been reported. A few studies showed that patients had a more significant QoL impairment when lesions were located on visible sites (e.g. face, neck and hand) [10, 11] whilst other studies did not find any relationship [12, 13]. By contrast, some studies report vitiligo lesions on more central body parts (e.g. chest, arms and trunks) are more likely to have an adverse impact on emotional wellbeing of people with the condition, perhaps because there remains anxiety as to how they might be judged by others if the condition were to be revealed [7, 14]. Indeed, the nature of reactions received from others is also likely to play an integral role in adjustment and the extent to which stigmatisation is experienced [15, 16]. Additional data from mixed method studies is needed to further understand this topic and how this may affect the possible comorbid burden of mental health conditions.

There is currently a lack of large population-based studies providing reliable estimates of the risks of psychological comorbidities associated with vitiligo in the UK. A recent observational study using the UK-THIN database [17] highlighted the burden of depression in vitiligo patients and found a bidirectional relationship between the two conditions. However, the study did not explore the associations with other forms of psychological distress and did not use a validated definition for depression. An analysis of the depression risk on the populations of different ethnicity and location of the vitiligo lesions, which can be potential sources of heterogeneity, were also not conducted.

## Objectives

To the best of our knowledge, there has only been one large population-based study assessing psychosocial comorbidities in vitiligo compared to those without the condition.[17] This study was limited only to exploring major depressive disorder (MDD, also termed recurrent depressive disorder) and used an unvalidated case definition for MDD. There have been no large-scale population studies looking at the association between vitiligo and depressive episodes (not meeting the criteria for MDD), anxiety, social phobias and other potential psychological complications of vitiligo. No current study explores the relationship with ethnicity and psychological outcomes or the associations between vitiligo location and a broader range of psychological outcomes beyond MDD. The aim of this study is therefore to fill this evidence gap.

We will conduct a large population-based study in the UK to determine the risks of comorbid mental health conditions (including depression, anxiety and other potential psychological complications of vitiligo) in people with vitiligo compared to control and to evaluate whether the relative risks may vary by different ethnicity. Reliable population-based estimates of the psychological burden associated with vitiligo are important to gain a better understanding of the condition and to ensure patients of different characteristics are provided with appropriate psychological support following diagnosis.

### Primary objectives

- Briefly describe the epidemiology of vitiligo in the dataset: vitiligo incidence of vitiligo over time and by age, sex, ethnicity and sociodemographic factors and lifetime prevalence by age and sex.
- Describe the prevalence of common mental health conditions (depressive episodes, recurrent depressive disorder and anxiety disorder), overall and stratified by sociodemographic factors and location of lesion, in adult patients diagnosed with vitiligo in a contemporary real-world population compared with matched controls without vitiligo
- Describe the incidence of common mental health conditions (depressive episodes, recurrent depressive disorder and anxiety disorders), overall and stratified by sociodemographic factors and lesion location, in adult patients diagnosed with vitiligo in a contemporary real-world population compared with matched controls in the first two years after vitiligo diagnosis.
- Describe current primary care service utilisation (primary care visits) and management patterns (secondary care referrals) in people with vitiligo with and without mental health conditions.

### Secondary objectives

- Describe the baseline prevalence and post diagnosis incidence of other potential psychological or work-related complications of vitiligo. These will comprise; time of work for illness, unemployment, social phobia, adjustment disorder, substance abuse, self-harm, overdose, and parasuicide or suicide attempts.

## Methods

### Data source

This study will use routinely collected and collated data from the Optimum Patient Care Research Database (OPCRD). This database incorporates pseudonymised primary care records from up to 700 GP practices distributed across England, Wales, Scotland and Northern Ireland. The current OPCRD cohort size is over 5 million actively registered people, and historic records available for 10.1 million people. The cohort dataset can be enhanced through direct-to-patient and direct-to-care provider questionnaires.

### Study design

The study will use the retrospectively collected data of all eligible patients within OPCRD at the date of data extraction. Within this primary care cohort, all patients with vitiligo will be identified using Read diagnostic codes. A diagnostic algorithm will be used to facilitate robust case identification vitiligo. This will comprise the identification of anyone with a vitiligo specific diagnosis code followed by exclusion of anyone with a diagnosis code for an alternative depigmenting disorder coded within a one-year period (six months before or after their first vitiligo diagnosis code). The list of alternative depigmenting disorders is shown in table 1.

Condition group	Conditions/causes included
Congenital and genetic hypomelanoses	Piebaldism Tuberous sclerosis Hypomelanosis of Ito Waardenburg syndrome Hermanski-Pudlak syndrome Griselli syndrome Menkes syndrome
Post-inflammatory hypomelanoses	Post-inflammatory leukoderma including after Atopic eczema or Psoriasis Lichen planus Pityriasis alba Lichen sclerosus
Post traumatic leukoderma	Post traumatic leukoderma
Para-malignant hypomelanoses	Cutaneous T-cell lymphoma (mycosis fungoides) Melanoma associated depigmentation
Occupational/drug induced hypomelanoses	Occupational vitiligo Other induced hypomelanoses
Para-infectious hypopigmentation	Pityriasis versicolor (or tinea versicolor) <i>Leprosy*</i> <i>Leishmaniasis*</i>
Others	Melasma Morphoea Idiopathic guttate hypomelanosis Xeroderma pigmentosum Progressive macular hypomelanosis Nevus depigmentosus Cutaneous sarcoidosis

**Table 1.** Potential differential diagnoses for vitiligo which will be used as exclusion criteria if they appear as diagnoses in the medical record within six months of the initial diagnosis of vitiligo (six months before or after the vitiligo diagnosis). \*As these conditions are extremely uncommon in the UK they will not be used in the exclusion process

The eligible vitiligo cases will comprise all incident cases of vitiligo over the last 15 years (2004-2020). Sociodemographic details will be extracted for all these cases and matched controls (described below). Sociodemographic data will comprise age group, gender, ethnicity, and socioeconomic status. Ethnicity will be categorised as follows to be consistent with the UK official census categories: White, Asian, Black African/Caribbean, Mixed, and Other. The index of multiple deprivation (IMD) will be used as a measure of socioeconomic status. This is derived from postcode at the point of data extraction and is available for nearly all patients contributing data.

Each incident case of vitiligo will be matched with an unaffected control (people without vitiligo at the date of matching) using propensity score matching (matching on the sociodemographic

variables list above and matching within primary care practice where numbers allow). The mental health conditions proposed to be examined are listed in table 2.

In addition, we will also explore whether the presence of a mental health condition at vitiligo diagnosis is related differences in service utilisation/management. We will describe the potential association between the presence of a mental health condition at vitiligo diagnosis and whether this is associated with increased primary care visits or an increased chance of a secondary care referral to dermatology. We will compare primary care visits and secondary care referral rates over the first year after diagnosis in those with a depressive illness or anxiety disorder at baseline to those without using Cox proportional hazards models adjusted for sociodemographic factors and other potential confounders. We will also report the overall primary care visit frequency and secondary care referral rate for comparison.

Condition	Description
<b>Primary outcomes</b>	
<b>Depression</b>	Recurrent depressive disorder or treated depressive episode
<b>Anxiety</b>	Non-phobia related anxiety episodes or disorder
<b>Secondary outcomes</b>	
<b>Time off work for illness</b>	Issue of a Med 3 certificate of fitness for work – indicating time off work for illness or other coded evidence of time off work
<b>Unemployment</b>	Any primary care coded evidence of unemployment
<b>Social phobia</b>	Diagnosis of social phobias including agoraphobia
<b>Adjustment disorder</b>	Diagnosis of adjustment disorder
<b>Intentional Overdose</b>	Any recorded intentional overdose or self-poisoning episode
<b>Substance abuse</b>	Record substance abuse including cannabis, alcohol, opioids, cocaine, hallucinogens, hypnotic/anxiolytic agents, or other substances.
<b>Self-harm</b>	Any recorded code indicative of self-harm by any method
<b>Suicide attempt</b>	Any recorded attempted suicide or parasuicide episode

**Table 2.** The mental health and related conditions to be explored.

## Statistical methods

Standard descriptive statistics (mean, standard deviations, etc) will be used to describe the characteristics of the study cohort. The study will report the baseline prevalence (odds ratio) and incidence (hazard ratio) for each mental health condition in the vitiligo cases compared with controls. These outcomes will be compared between cases and controls in subgroups by gender and ethnicity. Within the vitiligo cohort the relationship between disease characteristics and the primary outcomes will be examined. Statistical significance for analyses will be reported using P values and 95% confidence intervals as appropriate.

## Adverse event reporting considerations

This query/analysis involves the use of retrospectively collected data of all eligible patient data that exist as structured data within the OPCRD by the time of query/ analysis start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

## Conclusions

This study will provide the first population-level analysis of the risk of multiple psychological comorbidities in people with vitiligo. The results will provide a measure of the magnitude of any associations. These insights will be invaluable for clinicians managing patients with vitiligo; highlighting in a much more detailed fashion than is already known the psychological impact of vitiligo. These findings will be facilitative in allowing early interventions to be targeted to those most at risk, thus potentially preventing the development of more serious mental health problems.

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