



Vitiligo: Epidemiology and Economic Impact

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ABSTRACT **Introduction:** Vitiligo is an acquired disorder of pigmentation, characterized by the development of white patches on the skin, often with a typical symmetrical distribution and progressive extension [1,2]. Although vitiligo does not cause direct physical impairment, it can produce a relevant psychosocial burden. Despite this burden, effective treatments are lacking, emphasizing the need for new therapeutic options.

Objectives: The aim of this study was to systematically scan the scientific literature for studies dealing with vitiligo epidemiology. Additionally, the study aimed to assess the social costs of vitiligo, ultimately raising awareness about the societal impact of the condition. The focus was on Italian data.

Methods: Our research employed a comprehensive methodology. For the epidemiology, we systematically searched PubMed database up to October 2023 and complemented the analysis with Real World Evidence. For social costs, we conducted an in-depth literature review, administered a web-survey to 20 Italian dermatologists and conducted an equivalent number of interviews during the same period in March 2022.

Results: The data suggest that in Italy the prevalence of vitiligo increases with age, and it varies from 0.19% (age 18-21) to 0.6% (age >45) [3,4]. We estimated 152,000 patients diagnosed with Non-Segmental Vitiligo (NSV) in Italy; based on Body Surface Area (BSA), 33% are Not Severe, 31% Mild, 27% Moderate/Severe, 9% Very Severe. The yearly social costs of vitiligo amount to €0.5Bln.

Conclusions: There is a remarkable association of vitiligo with anxiety and depression [5,6,7,8,9], and Mental Health is associated with 30% of social costs. Moreover, vitiligo social costs distribution highlights inequity, with patients bearing 55% of them.

Introduction

Vitiligo is a chronic autoimmune depigmenting skin disease that results in patchy loss of skin color due to the progressive destruction of melanocytes [1,10]; it is now widely accepted that vitiligo has an autoimmune nature. This condition is characterized by extended periods of stability interspersed with shorter periods of accelerated depigmentation [11]. Treatment remains a challenge in dermatology, as available options produce limited results [12,13].

Vitiligo is a prevalent global skin condition which affects equally both genders, though slightly more prevalent in females, and more than 60% of patients experienced disease onset before the age of 30 [14,15].

There are two main clinical phenotypes [16]: Non-Segmental vitiligo (NSV) and Segmental vitiligo (SV). NSV is the most common form, characterized by symmetrical lesions on both sides of the body, progressing slowly and unpredictably.

Vitiligo is frequently associated with various autoimmune comorbidities such as hypothyroidism and rheumatoid arthritis [17].

The psychological impact is substantial, negatively affecting patients' quality of life (QoL) and Mental Health [5,6,7,8,9,18,19]. Indeed, the stigma associated with vitiligo impacts personal lives and productivity, leading to poor self-acceptance and psychological distress [20]. Everyday activities are disrupted, causing considerable time and energy waste for patients and their caregivers. Patients commonly experience depression, anxiety, stigmatization, hopelessness, and loss of self-esteem [20,21].

Despite the substantial burden it places on individuals, there is still a notable unmet need for effective treatments, leaving patients frustrated and hopeful for the development of efficacious options.

Objectives

The goals of the study were to determine the prevalence of vitiligo in Italy, segment patients to understand treatment adoption and behavior, and assess the social costs associated with the condition. Moreover, the aim was to shed light on the economic and societal burdens of vitiligo in Italy.

Methods

Our research utilized a comprehensive methodology, encompassing web-surveys involving 20 Italian dermatologists (i.e., "Medical Survey") in March 2022, interviews with an additional 20 dermatologists during the same period, and an extensive desk research that scrutinized over 100 publications, articles, and industry reports. In particular, data collection included a broad range of sources, including Real-World

Evidence, scientific publications, public entities' websites (e.g., INPS, GU (Gazzetta Ufficiale)), scientific guidelines, national and regional NHS tariffs, statistics institutes (e.g., ISTAT, EUROSTAT), surveys, interviews, as well as information from company websites and the medical press.

Epidemiology

We systematically searched PubMed database up to October 4, 2023, with the following key words: epidemiology, prevalence, incidence, co-morbidities, risk factors. A total of 761 papers were retrieved and, after an eligibility assessment, only 82 were maintained. Out of these papers, 12 were systematic reviews summarising various aspects of the vitiligo epidemiology [5-9,25-28], and another 8 studies presented data on the epidemiology of vitiligo in Italy [3,4,29-35]. To avoid repetition and redundancy, we decided to focus on the above-mentioned studies only, i.e., systematic reviews and Italian data.

We then complemented the analysis through a bottom-up approach, using Real-World Evidence [36]. Lastly, we established patient classes for Non-Segmental vitiligo (NSV) based on clinical and demographic characteristics and validated these classifications through expert interviews.

Social Cost

We assessed both healthcare and non-healthcare costs associated with vitiligo. Among healthcare costs, we examined three components:

- **Vitiligo Treatment:** through the Medical Survey, we investigated the treatment behavior within distinct patient classes, specifically focusing on topical treatments, phototherapy, depigmentation, and surgery. We further quantified the costs associated with each treatment, using publicly available sources. Both NHS and patient costs were considered.
- **Autoimmune Comorbidities:** our study delved into the prevalence of autoimmune comorbidities among vitiligo patients, including conditions such as hypothyroidism, rheumatoid arthritis, and inflammatory bowel disease. For each of these comorbidities, we examined literature on both direct and indirect associated costs.
- **Mental Health Conditions Assessment:** we explored the prevalence of Mental Health comorbidities, such as depression and anxiety, in vitiligo patients and their caregivers, as reported in the literature.

On the non-healthcare cost front, we assessed two components:

- **Non-Drug Products:** through Medical Survey, we examined the usage of non-drug products (e.g., make-up/concealer, self-tanners, sunscreen) within different patient

classes. Other direct costs were also considered (e.g., transportation expenses).

- **Indirect Social Costs:** our study included an estimation of the time allocated for treating vitiligo and Mental Health comorbidities within each patient class. We also evaluated the influence of Mental Health comorbidities on employment status.

Results

Epidemiology

Here we present eight Italian studies with a clear epidemiologic design [3,4,29-35].

In the *Praktis study*, conducted between March 1, 2003, and April 30, 2004, a random sample of 12,483 Italian subjects aged 45 or older was collected and interviewed, showing a 0.6% lifetime prevalence of physician-diagnosed vitiligo, with no difference according to gender and an increasing prevalence with age [29].

The *Epienlist project*, carried out by the Department of Dermatology at the Italian Navy Hospital in Taranto, examined 23,468 potential conscripts in southern Italy, aged 18-21. Those with skin lesions were referred to the hospital for diagnosis. The point prevalence of vitiligo was 0.19% [3]. Quality of life was assessed for 40 vitiligo patients, with a mean Dermatology Life Quality Index (DLQI) score of 1.82 [33]. Analysis revealed that only lesions on the hands (OR:6.32) and face (OR:5.03) significantly influenced the mean DLQI.

A survey of quality of life was conducted on 181 consecutive vitiligo patients at a single institution in Rome, using the Skindex-29 tool [30]. The problems more frequently experienced were worry of the disease getting worse (60%), anger (37%), embarrassment (34%), depression (31%).

Another survey of quality of life using DLQI was conducted on a sample of 161 vitiligo patients referred to 9 dermatological departments in Italian hospitals [34]. The mean total DLQI score was 4.3 (SD±4.9; range: 0-22). In multivariate analysis, DLQI >5 was associated with female gender, stability of the disease and involvement of the face at disease onset.

In a survey conducted during spring 1997, a total of 3,179 schoolchildren attending secondary schools in Italy were assessed through a questionnaire filled in by their parents [31]. The reported prevalence of vitiligo was 0.06%.

The *EDEN Fragrance study* enrolled 2,035 randomly sampled individuals aged 18 or older in Italy. Clinical examinations and patch tests were conducted. The lifetime prevalence of vitiligo was 0.4%, with no significant gender difference [35].

The prevalence of vitiligo in Italy, as determined by the studies, falls within the range of 0.19%-0.6%, increasing with age.

In addition, an Italian ReS Real-World Evidence study [36] was considered. This study examined the number of patients undergoing phototherapy treatment for vitiligo from 2013 to 2018 and revealed that 0.06% of the patient population received such treatment during that period. Employing a bottom-up methodology, we expanded the study's scope to incorporate patients who underwent phototherapy prior to 2013 or received alternative treatments, to ensure a complete understanding of the vitiligo-diagnosed population. We then added undiagnosed cases (41%) [35] to derive a lifetime vitiligo prevalence rate of 0.55%, which is in line with that reported by literature.

Considering that only 15% of vitiligo cases are Non-Segmental vitiligo (NSV) [37-40], we estimated a total of 279,000 NSV patients in Italy in 2022. Among these, 152,000 received a diagnosis, with 33% classified as having BSA <0.5% (Not Severe at all), 31% with BSA 0.5%-3.5% (Mild), 27% with BSA 3.5%-10% (Moderate/Severe), and 9% with BSA >10% (Very Severe) [41].

Vitiligo Treatment Cost

The costs of vitiligo treatment include all direct medical expenses, including therapies, examinations, laboratory tests, and supplements. NSV treatment rate varies among patient segments. Treatment rate tends to be higher in more Severe forms of NSV: only 35% of Not Severe NSV patients receive treatment compared to 84% of Very Severe NSV patients. Within the same Moderate-Severe segment, adolescents and females exhibit a relatively higher treatment rate (81% and 80% respectively) compared adult males (70%).

For each patient class, treatment preferences were examined through the Medical Survey: preferred options for cases of lower severity included topical corticosteroids and calcineurin inhibitors, while in Moderate-Severe cases, phototherapy and systemic corticosteroids were preferred (Figure 1).

To compute costs, we identified the most used molecules and their average therapeutic regimens, and we distinguished between costs in private and public settings (Table 2). According to the Medical Survey, 49.5% of patients are treated in public, and 50.5% in private settings. Then, considering the specific needs of each class of NSV patients, we added costs for dermatologist and nutritionist examinations, blood/urine tests, and supplements.

Total medical costs for NSV patients amount to €80Mln and the large majority (95%) is covered by the patient. Costs consist of treatments (35%) and supplements (38%), followed by medical examinations (23%) and lab tests (4%). The annual treatment cost per patient ranges from €208 for Not Severe cases to €906 for Moderate/Severe adolescents.

Autoimmune Comorbidities

In a retrospective study, 15.3% of patients with vitiligo had one or more significant comorbid autoimmune condition,

Table 1. Summarization of data from relevant Italian studies.

First Author	Publication	Focus	Study size	Results
Naldi [29]	2004	Lifetime prevalence	Random sample of 12,483 Italian citizens aged >45	Lifetime prevalence 0.06% with no difference based on age and sex
Ingordo [3]	2007	Point Prevalence	23,468 conscripts in southern Italy, aged 18-21	Point prevalence 0.19%
Sampogna [30]	2008	Quality of life	181 consecutive vitiligo patients at a Roman institution, using Skindex-29 tool, 12-item General Health Questionnaire	Problems frequently experienced: worry of getting worse (60%), anger (37%), embarrassment (34%), depression (31%). The prevalence of patients with probable depression or anxiety was 39%
Naldi [31]	2009	Risk factors and diseases associated with atopic dermatitis	3,179 schoolchildren aged 12-17 years	Lifetime prevalence of vitiligo 0.6%
Ingordo [32]	2011	Autoimmunity in vitiligo	40 conscripts with vitiligo systematically assessed for autoantibodies and history of immune-related disease	Circulating autoantibodies detected in 42.5% of subjects
Ingordo [33]	2012	Quality of life	40 conscripts with vitiligo assessed through DLQI	Mean total DLQI score 1.82 (SD± 2.95; min/max: 0-13). The localization on the hands (OR:6.32) and on the face (OR:5.03) influenced significantly the mean DLQI
Ingordo [34]	2014	Quality of life	161 vitiligo patients referred to dermatological departments in Italy assessed by DLQI	DLQI score 4.3 (SD ±4.9; range: 0-22). In multivariate analysis, DLQI >5 was associated with female gender, stability of the disease over time and involvement of the face at disease onset
Svensson [35]	2018	Lifetime Prevalence of vitiligo in a survey on contact dermatitis	Random sample of 2,035 people aged >18 in Bergamo	Lifetime prevalence of vitiligo 0.4% with no significant difference according to gender

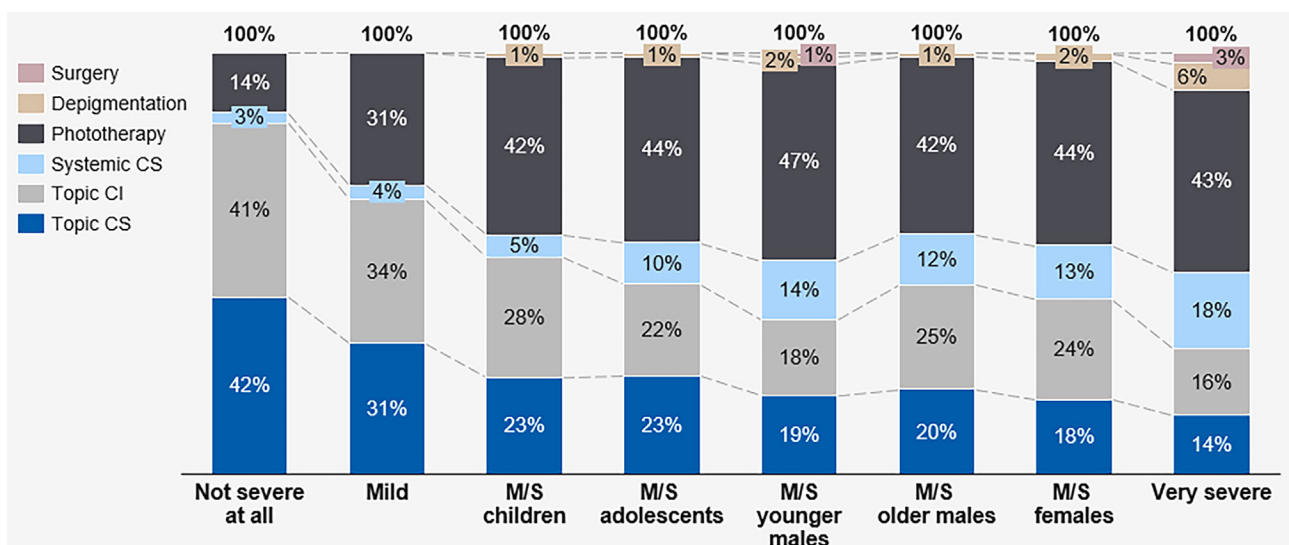


Figure 1. NSV Treatment Preference by Patient Class (%)

Table 2. NSV treatment options costs (€, yearly).

	Overall cost	Of which on patient	Of which on NHS
Induction therapy CS systemic (\pm TCS)	351	192	159
Induction therapy TCS	291	192	99
Induction therapy TCI	461	236	225
Maintenance therapy TCS (lower dose)	84	55	29
Maintenance therapy TCI (lower dose)	200	102	97
UVB phototherapy (e.g., NB-UVB, excimer laser)	4,077	3,947	130
UVB phototherapy + TCS or TCI	4,198	4,014	184
PUVA	4,373	4,247	125
Candidate for surgery (scheduled/operated)	2,488	33	2,454
Depigmentation	800	800	-

Table 3. Disease costs for selected autoimmune diseases (€, yearly).

	Overall cost	Of which direct cost	Of which indirect cost
Hypothyroidism	953	250	702
Rheumatoid arthritis	12,341	5,891	6,450
Inflammatory bowel disease	3,032	2,817	215
Lymphoma	52,992	47,004	5,988
Systemic lupus erythematosus	18,574	2,637	15,937
Seronegative arthritis	12,341	5,891	6,450
Idiopathic thrombocytopenic purpura	8,417	7,294	1,123
Multiple sclerosis	38,000	17,351	20,649
Pernicious anemia	393	103	289
Myasthenia gravis	14,950	12,160	2,790

Table 4. Direct costs associated to Mental Health.

	Overall cost	Of which on patient	Of which on NHS
Depression treatment	2,879	374	2,504
	Overall cost	Of which on patient	Of which on NHS
Anxiety treatment	2,431	615	1,816
	Overall cost	Of which on patient	Of which on NHS
Psychotherapy session	76	76	~0

with hypothyroidism and rheumatoid arthritis being the most common [17]. Vitiligo patients incur direct and indirect costs due to autoimmune comorbidities [42-53]. Direct costs include healthcare and non-healthcare costs (e.g., inpatient care, drug costs, tests, transportation). Indirect costs include productivity losses due to morbidity/mortality, borne by the individual, family, society, or the employer (e.g., sick leave, early retirement). Indirect costs were assessed by the human capital approach (HCA) and the friction cost approach (FCA).

Mental Health Costs

According to a systematic review on psychosocial effects of vitiligo [3,15,23,54,55], disorders including or related to

Major Depressive Disorder (MDD) and anxiety (referred to as Generalized Anxiety Disorder, Social Phobia, Specific Phobia, Post-Traumatic Stress Disorder, Agoraphobia, Agoraphobia with Panic Disorder and Panic Disorder) were the most reported. Moreover, patients with vitiligo recur to psychotherapy more often than the general population.

We argue that the cost of mental health issues can be part of the overall cost of vitiligo. This is because the increased psychological distress in this group mostly arises from the difficulties caused by the disease itself. Therefore, we collected literature evidence for direct costs of depression (i.e., costs for residential structures, psychiatry-related tests, hospitalizations, antidepressants [55, 56]), costs for anxiety

Table 5. NSV non-drug costs (€).

	Cost of products (€ monthly per patient)	Cost of products (€ yearly per patient)
Concealers/Make-up	13	150
Self-tanners	12	140
Sunscreen	46	285
	Cost of transport (€ for occasion)	Cost of transport (€ yearly per patient)
Transport for testing/examinations	8	18-38
Transport for phototherapy	6	824
Transport for surgery	12	12

(drugs, hospitalizations, outpatient care, medical devices [57,58]) and costs for public and private psychotherapy.

Factors associated with a higher burden of psychosocial comorbidities include female sex, greater body surface area involvement (i.e., severity), and younger age. Our analysis shows that Moderate-Severe NSV females are the group with the highest spend in Mental Health (1,171€/year), followed by Very Severe NSV (1,157€/year) and Moderate-Severe older males (1,145€/year). Interestingly, another group affected by vitiligo-induced Mental Health issues are the caregivers of children and adolescents, spending approximately 1,062€/year. The group spending less on Mental Health is children (642€/year), who are mostly unaware of their physical appearance.

Non-Drug Costs

Non-drug costs consist in purchases of skin products for vitiligo (e.g., professional concealers, sunscreen) exceeding the usual expenses associated with standard skincare, and transport costs specifically related to vitiligo disease (e.g., transport to reach phototherapy center). Research shows that make-up and concealers are mostly used by Moderate/Severe NSV females (65%), followed by Mild NSV cases (55%) and Moderate/Severe NSV adolescents (55%); sunscreen is widely used across patient classes, up to 95% among Very Severe cases.

The non-drug annual cost for diagnosed patient ranges from 117€/year for Not Severe cases to 789€/year for Moderate/Severe women.

Indirect Costs

NSV patients lose time managing their condition, giving up both work and leisure time. Additionally, NSV patients lose time due to mental health comorbidities, either for treatment (e.g., psychotherapy) or due to disabling symptoms (e.g., hospitalizations, lost workdays).

To assess indirect cost due to productivity loss, we opted for the human capital (HC) approach, which states that the

value of the HC is approximated by the value of an individual's earning, so that the period of absence from work due to illness/treatment is considered and valued by the achievable gross income [59]. The HC method does not address the issue of the categories not receiving any income (typically stay-at-home spouses, unemployed and students) [60] and their inclusion in indirect costs computation is at the researcher's discretion. To address the limits of HC method, in this study we valued the "unemployed lost time" at the value of governmental unemployed benefit (NASpI [61]); "Inactive caregivers' time" at the value of minimum domestic labor wage; "Time lost out of working time for vitiligo treatment" (e.g., ointment application, make-up) at the value of willingness to pay for an additional hour of leisure time vs. unpaid work [62], assuming that the burden of treatment is comparable to unpaid work. The data for this section comes from scientific publications, public entities' websites (e.g., INPS), statistics institutes (e.g., INSTAT).

Our analysis shows that the indirect costs associated to vitiligo amount to €91Mln/year: 30% of this cost (€31Mln) is associated to Mental Health (for either productivity loss related to treatment time or unemployment). The annual indirect social cost per diagnosed patient ranges from €288 for Not Severe cases to €1,182 for Moderate-Severe older males.

Conclusions

In summary, data indicate that vitiligo prevalence increases with age in Italy, ranging from 0.19% at 18-21 years to 0.6% after age 45. Real World Evidence-based prevalence was estimated at 0.55%. These figures align with the findings reported in systematic reviews and recent studies.

Analyzing five cost components, the annual social cost of vitiligo in Italy is €500 million, with costs per patient ranging from €2,200 to €4,600/year. Patients bear 55% of the cost, the NHS covers 18%, and 27% is borne by society. This distribution results in significant inequity, with over half of the social cost being paid directly by patients or caregivers.

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