



HAL
open science

Health-related quality of life, social and psychological well-being of 109 adult patients with genetic lipodystrophy

Hélène Mosbah, Camille Vatier, Corinne Vigouroux, Béatrice Andriss, Inès Belalem, Brigitte Delemer, Sonja Janmaat, Anne-Deborah Bouhnik, Lauriane Le Collen, Dominique Maiter, et al.

► To cite this version:

Hélène Mosbah, Camille Vatier, Corinne Vigouroux, Béatrice Andriss, Inès Belalem, et al.. Health-related quality of life, social and psychological well-being of 109 adult patients with genetic lipodystrophy. *Journal of Clinical Endocrinology and Metabolism*, 2024, <10.1210/clinem/dgae837>. <inserm-04772403>

HAL Id: inserm-04772403

<https://inserm.hal.science/inserm-04772403v1>

Submitted on 7 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization



HAL
open science

Health-related quality of life, social and psychological well-being of 109 adult patients with genetic lipodystrophy

Hélène Mosbah, Camille Vatier, Corinne Vigouroux, Béatrice Andriss, Inès Belalem, Brigitte Delemer, Sonja Janmaat, Anne-Deborah Bouhnik, Lauriane Le Collen, Dominique Maiter, et al.

► To cite this version:

Hélène Mosbah, Camille Vatier, Corinne Vigouroux, Béatrice Andriss, Inès Belalem, et al.. Health-related quality of life, social and psychological well-being of 109 adult patients with genetic lipodystrophy. *Journal of Clinical Endocrinology and Metabolism*, 2024, 10.1210/clinem/dgae837 . inserm-04772403

HAL Id: inserm-04772403

<https://inserm.hal.science/inserm-04772403v1>

Submitted on 7 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

- 1 **Title page**
- 2 **Title:** Health-related quality of life, social and psychological well-being of 109 adult patients with genetic
3 lipodystrophy
- 4 **Authors:**
- 5 Hélène Mosbah^{1,2,3}, Camille Vatie^{3,4}, Béatrice Andriss⁵, Inès Belalem³, Brigitte Delemer⁶, Sonja Janmaat^{3,4},
6 Anne-Deborah Bouhnik⁷, Lauriane Le Collen⁸, Dominique Maiter⁹, Estelle Nobécourt¹⁰, Marie-Christine
7 Vantyghem¹¹, Corinne Vigouroux^{3,4} and Agnes Dumas¹, on behalf of PRISIS network
- 8 Affiliations :
- 9 ¹Université Paris Cité, ECEVE UMR 1123, INSERM, Paris, France
- 10 ²Service Endocrinologie, Diabétologie, Nutrition, CHU La Milétrie, Poitiers, France
- 11 ³Hôpital Saint-Antoine, Centre de Référence des Maladies Rares de l'Insulino-Sécrétion et de l'Insulino-
12 Sensibilité (PRISIS), Service d'Endocrinologie, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France
- 13 ⁴Sorbonne Université, Inserm U938, Centre de Recherche Saint-Antoine et Institut de Cardio-Métabolisme
14 et Nutrition (ICAN), Paris, France
- 15 ⁵Unité d'Epidémiologie Clinique, APHP, Hôpital Universitaire Robert Debré, Paris, France.
- 16 ⁶Service d'endocrinologie diabète nutrition, CHU de Reims, Hôpital Robert-Debré, 51100, France
- 17 ⁷Aix Marseille Univ, INSERM, IRD, ISSPAM, SESSTIM, Sciences Economiques & Sociales de la Santé &
18 Traitement de l'Information Médicale, Equipe CALIPSO, Marseille, France
- 19 ⁸Univ. Lille, Inserm UMR1283, CNRS8199, European Genomic Institute for Diabetes (EGID), Institut Pasteur
20 de Lille, Lille University Hospital ; Lille, France ; Département de Médecine Moléculaire, Division de
21 Biochimie, Biologie Moléculaire, Nutrition et Métabolisme, Centre Hospitalier Universitaire de Nancy,
22 Nancy, France; Centre de Référence pour les Erreurs Innées du Métabolisme (ORPHA67872), Centre
23 Hospitalier Universitaire de Nancy, Nancy, France.
- 24 ⁹Service d'Endocrinologie et Nutrition, Institut de Recherche Expérimentale et Clinique IREC, Cliniques
25 Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgique
- 26 ¹⁰Service d'endocrinologie Diabétologie, Centre Hospitalier Universitaire Sud Réunion, 97410 Saint Pierre,
27 France
- 28 ¹¹CHU Lille, Endocrinologie, diabétologie et métabolisme, 59000 Lille, France ; Inserm U1190, 59000 Lille,
29 France; Univ. Lille, 59000 Lille, France.

© The Author(s) 2024. Published by Oxford University Press on behalf of the Endocrine Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com. See the journal About page for additional terms.

1 **Six Keywords (maximum):** lipodystrophy syndrome, quality of life, well-being, psychosocial impact, rare
2 disease, self-report

3 **Corresponding author's contact information :** Dr Héléna Mosbah, CHU Poitiers, Rue de La Milétrie, 86000
4 Poitiers. Helena.mosbah@gmail.com. ORCID ID : 0000-0001-7360-4209.

5 **Name and address of author to whom reprint requests should be addressed:** Dr Héléna Mosbah, CHU
6 Poitiers, Rue de La Milétrie, 86000 Poitiers.

7 **Disclosure summary:** All authors declare that there is no conflict of interest that could be perceived as
8 prejudicing the impartiality of the research reported.

9 **Funding sources:** This work was supported by institutional fundings from the French Ministry of Solidarity
10 and Health, Assistance-Publique Hôpitaux de Paris, Sorbonne University and by the Association Française
11 des Lipodystrophies (AFLIP), through a donation to the Association Robert-Debré pour la Recherche
12 Médicale (ARDRM).

13

14 **Abstract**

15 Introduction: Lipodystrophy syndromes are rare diseases characterized by a generalized or partial
16 lipoatrophic morphotype and metabolic complications. Data on health-related quality of life and impact
17 of genetic lipodystrophy on social or psychological well-being are lacking.

18 Patients and Methods: Patients with genetic lipodystrophy were recruited throughout the French national
19 reference network for rare diseases of insulin secretion and insulin sensitivity. Patients completed a self-
20 reported questionnaire exploring their physical, psychological and social well-being and perceived impact
21 of the disease. Descriptive analyses and comparison with general population norms were conducted.

1 Results: Out of 175 eligible patients, 109 (84% of women) were included, either with familial partial (n=93)
2 or congenital generalized (n=16) lipodystrophy. Health-related quality of life based on physical and mental
3 scores was significantly decreased as compared to the French general population of similar age and gender
4 ($p<0.001$ for both). Forty-one percent of patients reported moderate or severe depression and 69% dealt
5 with chronic pain. Half of respondents had taken tranquilizers, sleeping pills or antidepressants over their
6 life. Female participants with genetic lipodystrophy were more frequently unemployed due to health
7 issues as compared to the general population. Social discrimination was highly prevalent (73%), coming
8 in 34% of cases, from health professionals. More than half of affected women reported a very negative
9 impact of lipodystrophy on body image, significantly associated with depressive symptoms.

10 Conclusion: This study highlights the need of psycho-social support in patients with lipodystrophy. An
11 integrated approach and evaluation of psychological and physical symptoms by physicians should be made
12 available to organize specialized care and set up specific therapeutic educational programs.

14 Introduction

15 Lipodystrophy syndromes are rare multisystemic diseases characterized by a limited fat storage capacity,
16 resulting in, on the one hand, a peculiar morphotype with a generalized or partial absence of body fat,
17 and, on the other hand, insulin resistance and cardiometabolic complications with glucose tolerance
18 abnormalities, hypertriglyceridemia, metabolic dysfunction-associated fatty liver disease (MAFLD),
19 increased cardiovascular risk, and, in women, polycystic ovarian syndrome (1). These can result in end-
20 organ complications such as acute pancreatitis, hepatic cirrhosis, proteinuric renal disease, or cardiac
21 insufficiency (2).

22 Previous studies have reported the early onset of severe metabolic complications and risk of end-stage
23 disease in patients affected by lipodystrophy diseases (2,3). Yet, in line with the multisystemic character

1 of the disease and the lack of knowledge from non-expert physicians, patients with lipodystrophy
2 experience considerable diagnostic delays, estimated to be around 12 years in genetic forms (4).
3 Undiagnosed metabolic and/or organ complications can severely impact morbidity and mortality
4 associated with the disease (5). Lipodystrophy also strongly impacts the physical morphotype which could
5 lead to decreased self-esteem and to social discrimination. Previous observational studies, on limited
6 numbers of subjects, have highlighted mood illness, chronic pain, and altered quality of life in affected
7 patients (6–10). However, the social impact of lipodystrophy disease on education, work or income has
8 not been described. Due to dysmorphic features and hyperandrogenism in women, self-image is a major
9 concern, possibly impacting psychological and social well-being (8). Given the high number of specialists
10 involved in the patient's diagnostic journey (4), burden associated with treatment and care could be
11 important, but there is a lack of insight in understanding and improving this burden.

12 Lipodystrophy syndromes can be primary or acquired in origin, and present in a wide range of clinical forms
13 (1,3,11,12). Genetic lipodystrophy syndromes are monogenic diseases due to pathogenic variants in
14 several genes, which are primarily involved in adipocyte physiology (development and/or differentiation
15 of adipocytes, structure and/or functions of adipocyte lipid droplet, adipocyte metabolic regulations) (1,3).
16 At the clinical level, this results in the peculiar morphotype of affected patients, characterized by the
17 absence of body fat, affecting all or most body adipose depots (11). At the metabolic level, the decreased
18 capacity of adipose tissue to store excess energy leads to ectopic storage of lipids, resulting in insulin
19 resistance-associated complications. Genetic forms of lipodystrophy are usually classified based on fat
20 loss distribution from partial forms of lipodystrophy (familial partial lipodystrophy, FPLD) to generalized
21 lipodystrophy (congenital generalized lipodystrophy, CGL) (13). Subcutaneous fat loss and/or abnormal fat
22 distribution are key diagnostic features of lipodystrophy disorders. In the most common monogenic form
23 of FPLD, due to *LMNA* pathogenic variants (FPLD2 or Dunnigan syndrome), lipoatrophy of the limbs,
24 anterior abdomen and chest contrasts with the accumulation of facio-cervical adipose tissue and muscular

1 hypertrophy, giving patients a facial cushingoid appearance and android morphotype. In FPLD,
2 lipodystrophy and metabolic complications occur gradually around puberty. In CGL, generalized
3 lipoatrophy, present at birth, can be associated with metabolic complications which usually worsen during
4 puberty or the post-pubertal period. Facial appearance is marked by an often cachectic appearance and
5 exacerbation of bone structures (6,7).

6 This work was designed, in a large sample of patients, to assess the physical, social and psychological well-
7 being and perceived impact of disease and its treatments in a large cohort of patients with genetic
8 lipodystrophy.

9 **Patients and Methods**

10 **Study design**

11 We conducted a cross-sectional study using a self-reported questionnaire. Participants were recruited
12 between September 2021 and March 2022 through the French National Reference Network for Rare
13 Diseases of Insulin Secretion and Insulin Sensitivity (PRISIS), encompassing the whole country including
14 French overseas territories, and open to patients coming from French-speaking neighboring countries such
15 as Belgium. In each center, adult patients with genetic lipodystrophy syndromes (CGL or FPLD) were invited
16 to participate through an information letter sent by e-mail or postal service via their referent physician,
17 and/or through the French patient lipodystrophy association (AFLIP). Patients under the age of 18, as well
18 as those with acquired lipodystrophy or with insufficient fluency of the French language, were not eligible.

19 After reception of their informed consent, patients received access codes to complete an online self-
20 reported questionnaire. Patients who felt uncomfortable with the online format were proposed to fill out
21 a paper version of the questionnaire. Patients were included when they responded to at least one
22 outcome. We have specified the number of responses for each outcome. The majority of responders were
23 unrelated although 11 families were identified, representing 26 responders. In addition, another 26

1 patients with FPLD due to the *LMNA* p.(Thr655Asnfs*49) founder variant may be related, even if they did
2 not declare any familial relationship (Supplemental Table 1, Data Repository Reference Number:
3 10.13140/RG.2.2.28446.55363) (14).

4 **Ethical approval**

5 This study was approved by the INSERM's Institutional Review Board (no. 21-787) and consent was
6 obtained from patients according to national ethical and legal requirements. This research follows the
7 principles of the Declaration of Helsinki.

8 **Study outcomes**

9 The questionnaire included several standardized questionnaires and specific *ad hoc* items. It was reviewed
10 by the patient lipodystrophy association AFLIP, and consisted of two parts measuring outcomes related to
11 1) patients' physical and psychological symptoms and 2) social and psychological well-being and perceived
12 impact of lipodystrophy.

13 **1) Physical and psychological symptoms evaluated with specific standardized questionnaires:**

14 **Health Related Quality of Life (HRQoL)** was assessed using the French version of the Short Form-12 Health
15 Survey (SF-12) (15), a generic health status measurement instrument, which gives two health summary
16 scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), as well as its
17 8 sub-dimensions: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH) for
18 PCS; ViTality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH) for MCS. A higher
19 score corresponds to a better perceived quality of life.

20 **Depressive symptoms** were assessed through the Patient Health Questionnaire-9 (PHQ-9) scale, a widely
21 used instrument to assess the presence and levels of depressive symptoms over the past two weeks. This
22 scale consists of 9 items regarding depressive symptoms with a four-point Likert scale (0 = not at all, 1 =

1 several days, 2 = more than half of the days, and 3 = nearly every day) (16). The levels of depression were
2 categorized as none, mild, moderate, moderately severe and severe, based on scoring in the range of 0-4,
3 5-9, 10-14, 15-19, and 20-27, respectively (17). In our study, moderately severe and severe categories were
4 grouped and considered as severe.

5 **Chronic pain.** Severity and interference of pain with daily life functions were assessed through the Brief
6 Pain Inventory (BPI) questionnaire (18). The BPI asks patients to rate the intensity of pain during the last
7 24 hours at its worst, least, and average levels by using a numeric scale of 0 to 10. Each rating scale is
8 bounded by the words “no pain” at the 0 end and “pain as bad as you can imagine” at the 10 end. Using
9 similar scales of 0 to 10, patients are also asked to rate the extent to which their pain interferes with seven
10 QoL domains that include general activity, walking, mood, sleep, work, relations with other persons, and
11 enjoyment of life. These scales are bounded by the words “does not interfere” and “interferes
12 completely.” With these answers, BPI pain intensity and interference scales are calculated (19). Patients
13 are also asked to report location of pain and use of analgesics.

14 **2) Social and psychological well-being and perceived impact of the disease and its treatment evaluated** 15 **through different domains:**

16 **Social outcomes.** Impact of the disease on social well-being (education, employment and loan
17 accessibility), as well as perceived discrimination were derived from the GEDEPAC-2 questionnaire (20).
18 This questionnaire was previously designed to explore the well-being of adults suffering from a chronic
19 illness since childhood and its potential associated factors. Social well-being is assessed through
20 descriptive items, which are similar to those used in national surveys possibly allowing a comparative
21 analysis with reference data from the French general population adjusted for age and sex by indirect
22 standardization (qualitative variables) or z-scores (quantitative variables). Educational level and
23 occupational category were recoded into three categories: low, intermediate and high. More precisely,

1 educational level was defined by the highest diploma obtained, considering three levels as follows: 1) low
2 (below the diploma delivered at the end of high school, around 18 years of age); 2) medium (high school
3 diploma) or high (college degree such as bachelor or more). The perceived social impact of the illness was
4 assessed through different items explicitly citing the disease as the cause of a given social problem (e.g.
5 did you have difficulties during your schooling or professional career because of your disease?).

6 **Psychological outcomes.** Patients were asked about the perceived psychological impact of lipodystrophy
7 on their life, their use of psychological support, their supportive needs, their use of psychoactive
8 substances (smoking, drinking, use of tranquilizers and antidepressants).

9 **Treatment burden.** The Treatment Burden Questionnaire (TBQ) measures the psychological and social
10 burden related to treatment of chronic diseases. It is composed of 15 items rated on a Likert scale ranging
11 from 0 (no impact) to 10 (major impact) assessing the constraints associated with what patients need to
12 do to take care of their health (e.g. medication intake, drug management, self-monitoring, visits to the
13 physician, laboratory tests, lifestyle changes, administrative tasks to access and coordinate care). Mean
14 scores were measured for each item and summed into a global score, ranging from 0 to 150 (21).

15 **Body image.** The Body Image Scale (BIS), initially developed for patients with cancer (22), allows a
16 complete assessment of behavioral, affective and cognitive aspects of body image. Patients scored from 0
17 ("Not at all") to 3 ("Very much") on each question so the higher score indicates increasing dissatisfaction
18 with body image. Two questions were excluded from the original questionnaire because they did not apply
19 to our population. Two items were added specifically targeted towards patients with lipodystrophy,
20 assessing impact of metreleptin treatment and plastic surgery on body image. Total BIS score was
21 calculated using the eight original questions from the questionnaire. Finally, we added an independent
22 question asking for which part(s) of the body the patient expresses its dissatisfaction. Analysis was
23 reported for women given that morphological changes mainly impact female patients.

1 **Sexual life.** Female participants, who declared to have had sexual intercourse during the last 12 months,
2 were asked about their sexual life: pain during intercourse, pleasure and libido, as well as global
3 satisfaction about their sexual life (20).

4 **Sociodemographic and clinical factors**

5 The questionnaire also included descriptive clinical factors (i.e. body mass index, age at diagnosis of
6 lipodystrophy) and sociodemographic factors (i.e. gender, age, birthplace (Metropolitan France, Overseas
7 territory, Other), city of residency (current residency and during adolescence), personal and parental
8 educational level). The type of area of residency (rural, small urban, large urban) (23) was assessed using
9 the classification provided by INSEE (French National Bureau of Statistics). In another part of this self-
10 reported questionnaire (4), we asked participants about the age at first symptom and the age at diagnosis.
11 This allowed us to calculate the diagnostic delay.

12 **Genetic data**

13 Pathogenic variants, as determined by the ACMG criteria, were collected for participants (24), by their
14 referent physician.

15 **Statistical analyses**

16 Statistical analyses were conducted using R software (Version 4.2.0) and SAS software (Version 9.4).
17 Descriptive statistics of interval-scaled data were expressed as median and interquartile ranges (IQR) or as
18 mean and standard deviation (SD). For qualitative variables, chi-squared tests of independence or, if
19 expected frequencies were below 5%, Fisher's exact test, were used.

20 **Internal analysis.** We performed group comparison for type of lipodystrophy (CGL or FPLD), current age,
21 gender, birthplace, area of current and previous residency, educational and occupational category
22 (patients and parents) for all variables. We used unpaired Mann-Whitney U-tests for comparisons between

1 two groups, and Kruskal-Wallis tests for comparisons between more than two groups. For all analyses,
2 two-sided P values ≤ 0.05 indicated statistical significance. We used Spearman non-parametric tests for
3 correlation analyses. We also studied the potential correlations between the diagnostic delay and selected
4 scores, as well as phenotype-genotype correlations.

5 **External analysis.** Regarding the Health-Related Quality of Life (HRQoL), only data based on the SF-12
6 questionnaire are available at the individual level in the French general population for detailed
7 comparisons. We thus compared the patients' raw mean scores of the SF-12 scale to the mean scores
8 obtained from individual data in the latest French general population national 10-year health survey (25).
9 Standardized z-scores were computed based on the distribution by age and gender of each summary score
10 (PCS and MCS) in the general French population, to allow adequate comparisons.

11 For external analyses regarding the social outcomes extracted from the GEDEPAC-2 questionnaire, the size
12 and the prominence of female responders in our study only allowed to study the health-related
13 unemployment. A standardized incidence ratio (SIR) for being permanently unemployed because of health
14 (i.e. living with a disability pension) was calculated based on aggregated reference data issued from the
15 French general population matched by age and sex (26). Data were restricted to women aged 20-59 living
16 in France and with valid self-reported data on their employment status (n=69) to ensure data
17 comparability.

18 **Results**

19 **Study population**

20 Eligible patients were identified from participating centers (n=155) or recruited through the media
21 communication campaign (n=20), and 122 of them consented to fill out the questionnaire (Supplemental
22 Figure 1, Data Repository Reference Number: 10.13140/RG.2.2.28446.55363) (14). A total of 109 patients
23 returned the questionnaire and were included in the study (94 questionnaires were fully completed).

1 Sociodemographic and clinical data are summarized in Table 1. Genetic data are described in Supplemental
2 Table 1, Data Repository Reference Number: 10.13140/RG.2.2.28446.55363 (14). General characteristics
3 of the patients were previously described (4): 93 patients were diagnosed with FPLD (86% of women), 16
4 with CGL (75% of women). Patients with CGL reported being diagnosed at a younger age than patients
5 with FPLD. Respondents were 43 years old (median, IQR 30-55), younger in CGL than in FPLD group (29
6 years (25-44) versus 46 (32-56) respectively, $p=0.02$). The course of disease (i.e. the interval between the
7 current age and the age at diagnosis) was significantly higher in patients with CGL than patients with FPLD
8 (median IQR 22.6 (8.0-30.7) years versus 7.5 years (3.0-13.3) respectively, $p=0.005$). The majority of
9 respondents were born in metropolitan France (62%), 27% in French overseas territories and 11% outside
10 of France. Subjects with CGL lived more frequently in large urban areas and patients with FPLD in small
11 urban areas ($p=0.003$). Regarding clinical factors, median BMI was significantly lower in patients with CGL
12 than FPLD (25 versus 23kg/m² $p=0.02$).

13 **Physical and psychological symptoms in patients with genetic lipodystrophy**

14 ***Health-related quality of life***

15 Table 2 provides the scores for PCS, MCS and 8 subdomains, per gender, with a comparison of scores
16 between participants and the general population of the same age and gender. In the whole sample,
17 standardized mean physical and mental z-scores [IC95%] were -0.66 [-0.89;-0.44] and -0.71 [-0.95;-0.48],
18 respectively, significantly lower than those of the general population ($p<0.001$ for both). In female
19 participants with lipodystrophy, mean PCS and MCS, as well as the 8 subdomains scores were significantly
20 lower compared to the general female population, whereas in male, this was only the case for PCS and the
21 subdomain General Health (GH). In our cohort, mental scores were significantly worse in females than in
22 males, whereas there was no difference for physical ones.

23

1 **Depressive disorders**

2 Overall, the median (IQR) PHQ-9 score in patients with lipodystrophy was 8.0 (3.0-12.3) (Figure 1A).

3 Depression was rated as moderate in 21% of patients, and severe in 20% of patients (Figure 1B).

4 Distribution of PHQ-9 score was not different between male and female and not associated with age.

5 **Chronic pain**

6 Chronic pain was reported in 69% of patients with lipodystrophy, without significant difference between

7 FPLD and CGL. The distribution of painful parts of body is illustrated in Figure 2. Pain was mostly reported

8 in upper (25%) and lower (30%) limbs, without any significant difference between FPLD and CGL. Two-

9 third (59%) of patients with chronic pain reported a regular use of pain killer medications. Among

10 respondents with chronic pain, the median BPI intensity index (IQR) was 4.3 (3.0-5.8) (n=65) and the

11 median BPI index of interference with daily life functions was 4.1 (2.4-5.9) (n=67).

12 Social and psychological well-being, and perceived impact of the lipodystrophy disease and its treatment

13 **Social impact**

14 *Schooling.* Out of 106 respondents, 33 (31%) considered that they left school too early. For 22% of these

15 33 patients, this was related to their disease. Early school leaving was more frequent when the paternal

16 occupational category ($p=0.04$) or maternal educational level was low ($p=0.02$). Only one patient, affected

17 with CGL, had been educated in a school with special educational needs. For 23% of patients, the choice

18 of career was influenced by the lipodystrophy disease (62% with CGL versus 17% with FPLD, $p=0.001$).

19 Overall, among male and female patients, educational level was distributed as low (38%), medium (35%)

20 or high (27%) (Table 1). Among women living in Metropolitan France, a high educational level (bachelor's

21 degree or higher) was obtained in 47% of women aged 25-34 and 25% of women aged 45-54.

1 *Employment.* One quarter of respondents reported difficulties in finding employment. Of these, 58%
2 reported that their employment issues were due to their disease. In addition, employment difficulties were
3 increased in patients with a low occupational category ($p=0.01$). Nearly half of respondents (48/103) were
4 unemployed, of which 30% were unemployed due to health problems (receiving a disability pension). The
5 Standardized Incidence Ratio (SIR) [IC95%] for being unemployed due to altered health was 4.25 [1.10-
6 7.39] in female participants. One third of employed respondents (31/102) were formally recognized as
7 disabled workers. Two patients were working in a specific protected sector for disabled individuals.

8 *Discrimination.* In their life, 73% of LDG patients (76/104) reported that they had been mocked or treated
9 unfairly because of their physical appearance, illness or disability: 46% of patients reported disrespectful
10 behaviors coming from the school staff, 45% from friends, 42% from family members, 34% from health
11 professionals, 28% from work colleagues, 9% from employers. During their life, 54 patients among 103
12 (52%) had applied for a home or a professional loan. Among them, one third (16/51) had to disclose their
13 illness to the insurer, and 27% (12/46) reported difficulty in accessing loan-related insurance due to their
14 disease.

15 ***Psychological impact***

16 Overall, 61% (62/101) of patients reported a negative psychological impact of the disease in their life, 44%
17 of respondents consulted a psychologist and 39% (40/101) self-reported that they should have needed
18 more psychological support. The active smoking status concerned 40 % of respondents (41/102). Regular
19 (weekly) alcohol consumption was reported by 20 % of patients (29/102). Half of respondents (51/103)
20 resorted to medication such as tranquilizers, sleeping pills or antidepressants over their life.

21 ***Treatment burden***

22 Regarding results for the TBQ, median global score (IQR) was 38.0 (15.8-72.5) and mean global score (SD)
23 was 44.3 (2.9) ($n=100$). The highest burdens were related to the mental load of the illness and to efforts

1 following dietary advices. Conversely, the impact on social life related to taking medications was reported
2 as low. Detailed results of TBQ are depicted in Figure 3.

3 **Body Image**

4 Figure 4A shows the response rate and prevalence to individual questions of the Body Image Scale (BIS) in
5 female participants. More than half of women rated “very much” the following items: “less physically
6 attractive” (55%), “dissatisfied with body” (53%), “difficult to see oneself being naked” (52%), “self-
7 conscious about appearance” (52%). In 50% of women, metreleptin therapy did not improve body self-
8 image (n=11 among 22). After plastic surgery, 72% of women (n=24 among 33) reported to be
9 “moderately” or “very much” improved in their body appearance. In 80% of patients, at least one part of
10 their body made them uncomfortable. In women with CGL (Figure 4B), lower limbs were the body part
11 most frequently associated with a feeling of discomfort (25% of responders), followed by facio-cervical
12 region (22%), buttock and trunk (16%). Women with FPLD (Figure 4C) felt uncomfortable with their facio-
13 cervical region (33%), lower limbs (24%) and trunk (16%). The total BIS score was positively correlated with
14 the total PHQ-9 depression score ($r=0.46$, $p<0.0001$), and with the pain intensity and interference scores
15 (respectively, $r=0.26$ $p=0.04$, and $r=0.37$ $p=0.002$). The total BIS score was significantly higher in women
16 who reported disease-linked social discrimination compared to those who did not (median (IQR): 21 (10-
17 24) versus 8 (2-20), $p=0.004$).

18 **Sexual life**

19 For female participants (who declared to have had sexual intercourse during the last 12 months), sexual
20 intercourse was painful in 61% (28/46) of cases. In 87% (40/46) of female participants, sexual desire was
21 reported as insufficient or absent. Sexual pleasure was impaired in 86% (37/43) of female participants. In
22 total, 42% of women (22/52) were little or not satisfied with their sexual life.

23

1 ***Diagnostic delay and psychological impact***

2 We performed correlations analysis between diagnostic delay and selected scores: depression score
3 (n=84), body image scale score (n=88), total TBQ score (n=84). We did not find any significant association
4 between all these parameters.

5 ***Genotype-phenotype correlations***

6 We looked at whether patients with FPLD and patients with CGL (with known genotype) differed in terms
7 of quality of life (n=89), depression score (n=85), body image scale score (n=89), bodily pain scores (n=55),
8 and total TBQ score (n=83). There were no differences between the 2 groups, except for the vitality sub-
9 score in the SF12 questionnaire.

10 **Discussion**

11 By collecting self-reported data from more than 100 patients with genetic lipodystrophy, this cross-
12 sectional study provides a detailed overview on physical, mental and social well-being in patients affected
13 by these rare chronic diseases, compared to the general population. This is the first study exploring such
14 a large number of adult patients with genetic lipodystrophy, a rare but severe disease with
15 cardiometabolic complications and morphotype alterations. Our results show that health-related quality
16 of life is decreased in patients with genetic lipodystrophy in comparison to population norms and that the
17 prevalence of depressive symptoms is high, as also evidenced by the high frequency of psychotropic drug
18 use. Most patients suffer from chronic pain, which is probably largely underdiagnosed and should be
19 further investigated to specify its causes. Perceived impact of the lipodystrophic morphotype on social and
20 psychological well-being is significant, and affected patients' experience of social discrimination. This has
21 important consequences on their daily life, as measured by higher unemployment rates in female
22 participants with lipodystrophy as compared to women from the general population. Body image is
23 severely affected in female patients and contributes to the physical, mental and social burden of the

1 disease. We will now discuss those results in the light of other clinical studies performed in patients with
2 lipodystrophy, or of surveys conducted in the French general population.

3 Recently, data on quality of life using the Short-Form-36 (SF-36) questionnaire and systematic psychiatric
4 assessments in a population of patients with lipodystrophy (n=67, 61% FPLD, 24% CGL) living in Turkey
5 found decreased HRQoL scores in comparison to the Turkish general population, and reported that over
6 25% of patients with lipodystrophy presented with psychiatric disorders (9). In our work, health-related
7 quality of life was differently impacted depending on gender: it was strongly affected in women with
8 lipodystrophy, with decreased physical and mental scores, whereas men only reported a significantly
9 decreased physical health score, as compared to the French general population.

10 Our study points to mental health being severely affected in patients with lipodystrophy, with around 40%
11 of participants suffering from moderate or severe depression. These results are in line with data of the
12 Turkish cohort where 37% of patients reported a high score on the Beck Depression Inventory, associated
13 with major depression, at the first visit (5,9). In the study of Ajluni et al dedicated to efficacy of metreleptin,
14 52% of patients with partial lipodystrophy were reported to suffer from mood disorder (10/12 depression,
15 6/12 anxiety) (7). In a Reunionese group of 78 patients with genetic lipodystrophy, between 44% and 67%
16 of patients reported depressive symptoms (27). A psychiatric assessment should be warranted in all people
17 affected with lipodystrophy in order to manage psychiatric symptoms which severely impact mental well-
18 being. Indeed, in our study, around 40% of participants declared missing psychological support. Half of the
19 patients from our study have used tranquilizers and/or antidepressants. In comparison, in France, in 2017,
20 for women aged 35-44 and 45-54 years, this prevalence reaches respectively 21% and 28% over one year
21 (28).

22 Lipodystrophic diseases are primary diseases of adipose tissue that are associated with altered production
23 of adipokines, especially leptin and adiponectin (1,3,11–13), that, through their central actions, could also

1 contribute to depressive symptoms. Leptin not only interacts with central neuronal pathways to promote
2 satiety, control energy expenditure and regulate neuroendocrine hormonal responses, in particular those
3 involved reproductive functions, but it also influences the mesolimbic dopaminergic system and regulate
4 the hedonic aspects of feeding (29,30). Functional MRI studies performed in patients with lipodystrophy
5 have shown that leptin modify brain connectivity in hedonic and homeostatic central nervous networks
6 (31,32). Observational studies have also shown that substitutive treatment with metreleptin in patients
7 with lipodystrophy was associated with improved health self-perception (n=20 patients) (33) and with
8 reduction in the Beck's Depression Inventory score (n=10 patients) (34). Although many factors, including
9 metreleptin-associated changes in morphotype, could be involved, the contribution of a direct role of
10 leptin deficiency in depressive symptoms of patients with lipodystrophy cannot be ruled out. In addition,
11 adiponectin deficiency could also play a role, through central effects (35–37).

12 Despite the high cardiovascular risk in these patients, active smoking status is reported in as high as 40%
13 of our cohort, which is globally higher than in the French general population based on epidemiological
14 data from 2022 (32% in people aged 18-75) (38). Efforts in health care interventions that promote and
15 support smoking cessation in these patients will help to achieve a maximum health benefit (2). The self-
16 reported frequency of regular alcohol consumption was 20% in our study, inferior than in the general
17 French population (39% in 2021) (39), but significant in view of the risk of liver cirrhosis related to the
18 disease.

19 Concerning physical health, in our study, two-third of participants suffered from chronic pain requiring
20 analgic drugs on a regular basis. In the study of Ajluni et al, 78% of patients with partial lipodystrophy
21 reported chronic pain linked to neuropathy, arthralgia or myopathy (7). Qualitative interviews of 21
22 patients with lipodystrophy from the US demonstrated that pain was spontaneously reported as a
23 bothersome symptom in 62% of them (10). In the Reunionese group of patients with FPLD2, muscle pain
24 and fatigue affected between 30 and 64% of patients (27). Nevertheless, the self-reported scores of pain

1 in our study (level of severity and impact) were lower than those found by Tan and colleagues reporting
2 on 440 patients with chronic pain of diverse origin (except cancer) (19). Chronic pain is probably mainly
3 due to 1) fat loss, 2) muscle disease associated with lipodystrophy, and/or 3) peripheral neuropathy as
4 demonstrated by the distribution of painful parts of the body described by our study participants, which
5 pointed to inferior limbs in 30% of cases. Referral to pain centers, use of physiotherapy, drugs targeting
6 neuropathic pain, or non-specific analgesic are important in the disease management in patients with
7 lipodystrophy.

8 In our study, only 47% of female participants aged 25-34 had obtained a bachelor's degree as compared
9 to 54% in the French population of the same age and gender (26). Given that self-reported surveys are
10 usually filled out by the most educated participants (40), this lower educational level in women with
11 lipodystrophy could suggest that the disease induces social inequalities. Half of the participants, mainly in
12 their forties, were not working, lipodystrophy being associated with a 4-fold higher risk of being
13 unemployed in women, i.e., dependent on a disability pension for living, as compared with the French
14 general population. Nevertheless, in patients with a job, repartition of occupational category was similar
15 than in the French population (41). Negatively perceived impact of the illness on education or work was
16 reported by a third and a quarter of participants, respectively. Career path choice was significantly more
17 influenced by illness in CGL than in FPLD. This is likely due to the natural history of the disease beginning
18 in childhood in patients with CGL. The proportion of patients with lipodystrophy reporting discrimination
19 was high (73%) in comparison with 23% of individuals living with a disability reporting discrimination in the
20 French general population (42). In women with lipodystrophy, report of discrimination was associated with
21 altered body image. In one-third of the respondents, discrimination came from health professionals.
22 Raising awareness among health professionals is therefore a priority issue, as well as improving knowledge
23 about these rare diseases (4).

1 About a third of patients reported difficulties in accessing loan-related insurance in their life, which is
2 comparable to the proportion reported in adult survivors of childhood cancer in France (43). Since 2022,
3 in France, access to loan-related insurance is possible for all the people living with chronic and/or rare
4 diseases, under a certain age and a given amount, which helps to reduce the social inequalities generated
5 by disease.

6 Burden of the disease could participate to the mental health impairment as measured by TBQ. The highest
7 burden was associated with the mental load of the illness and the efforts needed to follow dietary
8 recommendations. Medication intake is burdensome considering the high number of daily drugs used by
9 patients with lipodystrophy (for diabetes, hypertension, dyslipidemia, cardiovascular disease, pain).
10 Dietary measures are considered as the basis of treatment since any excess of energy intake leads to
11 ectopic storage of fat and worsening of metabolic complications.

12 Body image is severely affected in women with lipodystrophy, as illustrated by our study. More than half
13 of the women are severely impacted regarding perception of their body image. In women with FPLD, facio-
14 cervical region was the region most devaluated, in line with the typical accumulation of fat mass associated
15 with the disease. In women with CGL, the region most dissatisfying was “inferior limbs” followed by the
16 “facio-cervical” region, both impacted by fat loss. Altered physical appearance is an important symptom
17 causing psychological distress and low self-esteem as previously reported by patients of the Turkish cohort
18 (n=67), using only one question (9). Similar to our findings, the previous Lipodystrophy Patient and
19 Caregiver Survey (n=10 patients) reported that physical appearance was a barrier to developing new
20 relationships, leading to social isolation, and increasing feelings of anxiety and depression (44). In a
21 previous work on care pathway in genetic lipodystrophy, hirsutism was reported by half of women,
22 possibly contributing to alteration of body image (4). In our present study, altered body image was
23 associated with the severity of depression. Access to plastic surgery should be systematically discussed
24 with patients, since a majority of respondents reported improvement of body image with surgery.

1 Our study presents the first data on overall physical, psychological and social well-being in a large number
2 of patients with genetic lipodystrophy. Mental illness previously described in patients with lipodystrophy
3 (6,9,27) may be a consequence of social stigma as shown by our results, although altered production of
4 adipokines could also lead to central effects. As health professionals are partly involved patients'
5 stigmatization, it seems essential to change practices and improve healthcare professional's education.
6 The opinion of patients themselves is provided, given the self-reported source of the data. The majority of
7 patients fully completed the questionnaire, which strengthens the study. Conversely to the previous study
8 on quality of life in lipodystrophy (9), only adult patients were included, which homogenizes the study
9 group. Unsurprisingly, women were more represented than men in our study. Misdiagnosis is frequent in
10 men since android morphotype and muscular appearance can be more easily considered as normal. As a
11 limitation of the study, it should be noted that analyses by gender were restricted because of the low
12 number of men in our sample. Indeed, regarding the social outcomes, the size and prominence of female
13 responders only allowed to precisely study the health-related unemployment of patients in comparison
14 with the French general population. To overcome this limitation for other social outcomes, we included
15 results extracted from surveys conducted in the French general population to discuss our results.

16 To conclude, efforts have to be made by physicians to improve their approach to the patients, and
17 systematically evaluate psychological and physical symptoms, in order to refer them to specialized care if
18 needed. Specific therapeutic educational programs should include systematically psychological and social
19 support. Development of rare disease networks working in cooperation with specialists is a key point given
20 the multisystemic character of the disease.

21

22

23

1 **Author Contribution**

2 HM, CVa, CVi, AD and designed and conducted the research. HM analyzed the data and wrote the
3 manuscript. BA setup the online questionnaire. IB, SJS, EN, MCV, BD, LLD, DM. The PRISIS network
4 participated to the collection of the data and to the design of the questionnaire: Pr Sophie Béliard, Dr
5 Claire Briet, Dr Bruno Donadille, Dr Noémie Dubois, Dr Olivier Gilly, Dr Stéphanie Jellimann, Dr Julie Maître,
6 Pr Yves Reznik, Dr Frédérique Rimareix, Pr Bruno Vergès. All authors made substantial contributions to
7 conception, design, acquisition of data, data analyses and data interpretation. All authors revised the
8 manuscript critically for important intellectual content and gave their approval of the final version to be
9 published. HM and AD are the guarantor of this work and takes responsibility for the integrity of the data
10 and the accuracy of data analysis.

11 **Acknowledgments**

12 We thank the patients who participated in this study, and the AFLIP French patient lipodystrophy
13 association for its scientific and funding contribution. Corinne Vigouroux represents PRISIS in the European
14 Reference Network on Rare Endocrine Conditions – Project ID No 739527. We thank Fallou Leye and Lisa
15 Duconget for their help in the data management and analysis, Sophie Guilmin-Crepon for the help in the
16 setup of the study.

17 **Data availability**

18 The datasets presented in this article are not readily available because of the sensitive nature of the data
19 and possible high risks associated with patient confidentiality. Requests to access the datasets should be
20 directed to camille.vatier@aphp.fr.

21 **References**

22 1. Lim K, Haider A, Adams C, Sleigh A, Savage DB. Lipodystrophy: a paradigm for understanding the
23 consequences of « overloading » adipose tissue. *Physiol Rev.* 2021;101(3):907-93.

- 1 2. Akinci B, Oral EA, Neidert A, Rus D, Cheng WY, Thompson-Leduc P, et al. Comorbidities and Survival
2 in Patients With Lipodystrophy: An International Chart Review Study. *J Clin Endocrinol Metab.*
3 2019;104(11):5120-35.
- 4 3. Zammouri J, Vatieer C, Capel E, Auclair M, Storey-London C, Bismuth E, et al. Molecular and Cellular
5 Bases of Lipodystrophy Syndromes. *Front Endocrinol.* 2022;12:1830.
- 6 4. Mosbah H, Vatieer C, Andriess B, Belalem I, Delemer B, Janmaat S, Jéru I, Le Collen L, Maiter D,
7 Nobécourt E, Vantyghem M.-C., Network « Pathologies Rares de l'Insulino-Sécrétion et de l'Insulino-
8 Sensibilité » (PRISIS), Vigouroux C., Dumas A. Patients' perspective on the medical pathway from first
9 symptoms to diagnosis in genetic lipodystrophy. *Eur J Endocrinol.* 2024;190(1):23-33.
- 10 5. Yildirim Simsir I, Tuysuz B, Ozbek MN, Tanrikulu S, Celik Guler M, Karhan AN, Denkboy Ongen Y,
11 Gunes N, Soyaltin U.E, Altay C, Nur B, Ozalkak S, Akgun Dogan O, Dursun F, Pekkolay Z, Eren M.A, Usta Y,
12 Ozisik S, Ozgen Saydam B, Adiyaman S.C, Unal, M.C, Gungor Semiz G, Turan I, Eren E, Kayserili H, Jeru I,
13 Vigouroux C, Atik T, Onay H, Ozen S, Arioglu Oral E, Akinci B. Clinical features of generalized lipodystrophy
14 in Turkey: A cohort analysis. *Diabetes Obes Metab.* 2023;25(7):1950-1963.
- 15 6. Calabrò PF, Ceccarini G, Calderone A, Lippi C, Piaggi P, Ferrari F, Magno S, Pedrinelli R, Santini F.
16 Psychopathological and psychiatric evaluation of patients affected by lipodystrophy. *Eat Weight Disord*
17 *EWD.* 2020;25(4):991-998.
- 18 7. Ajluni N, Dar M, Xu J, Neidert AH, Oral EA. Efficacy and Safety of Metreleptin in Patients with Partial
19 Lipodystrophy: Lessons from an Expanded Access Program. *J Diabetes Metab.* 2016;7(3).
- 20 8. Adams C, Stears A, Savage D, Deaton C. « We're stuck with what we've got »: The impact of
21 lipodystrophy on body image. *J Clin Nurs.* 2018;27(9-10):1958-68.
- 22 9. Demir T, Simsir IY, Tuncel OK, Ozbaran B, Yildirim I, Pirildar S, Ozen S, Akinci B. Impact of
23 lipodystrophy on health-related quality of life: the QuaLip study. *Orphanet J Rare Dis.* 2024;19(1):10.
- 24 10. Martin SA, Sanchez RJ, Olayinka-Amao O, Harris C, Fehnel S. Qualitative interviews in patients with
25 lipodystrophy to assess the patient experience: evaluation of hunger and other symptoms. *J Patient-Rep*
26 *Outcomes.* 2022;6(1):84.
- 27 11. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, Jack M, Mungai L, Oral E.A, Patni N, Rother
28 K.I, von Schnurbein J, Sorkina E, Stanley T, Vigouroux C, Wabitsch M, Williams R, Yorifuji T. The Diagnosis
29 and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. *J Clin Endocrinol*
30 *Metab.* 2016;101(12):4500-11.
- 31 12. Semple RK. EJE PRIZE 2015: How does insulin resistance arise, and how does it cause disease?
32 Human genetic lessons. *Eur J Endocrinol.* 2016;174(5):R209-223.
- 33 13. Patni N, Garg A. Lipodystrophy for the Diabetologist-What to Look For. *Curr Diab Rep.*
34 2022;22(9):461-70.
- 35 14. Dumas, A. (2024). Supplemental material (Figure S1 and Table S1) for "Mosbah et al., Health-related
36 quality of life, social and psychological well-being of 109 adult patients with genetic lipodystrophy"
37 (Provisory Version). Research Gate. doi: 10.13140/RG.2.2.28446.55363

- 1 15. Burdine JN, Felix MR, Abel AL, Wiltraut CJ, Musselman YJ. The SF-12 as a population health
2 measure: an exploratory examination of potential for application. *Health Serv Res.* 2000;35(4):885-904.
- 3 16. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the
4 PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire.*
5 *JAMA.* 1999;282(18):1737-44.
- 6 17. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J*
7 *Gen Intern Med.* 2001;16(9):606-13.
- 8 18. Stanhope J. Brief Pain Inventory review. *Occup Med Oxf Engl.* 2016;66(6):496-7.
- 9 19. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic
10 nonmalignant pain. *J Pain.* 2004;5(2):133-7.
- 11 20. Mellerio H, Dumas A, Guilmin-Crépon S, Loirat C, Lévy-Marchal C, Audard V, De Vathaire F, Alberti
12 C. Well-being in adulthood of patients with chronic conditions in childhood: The GEDEPAC-2 questionnaire.
13 *Rev Epidemiol Sante Publique.* 2017 Apr;65(2):137-148.
- 14 21. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of
15 measurement properties of an instrument to assess treatment burden among patients with multiple
16 chronic conditions. *BMC Med.* 2012;10:68.
- 17 22. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. *Eur J*
18 *Cancer Oxf Engl* 1990. 2001;37(2):189-97.
- 19 23. European Commission. Statistical Office of the European Union. Applying the degree of
20 urbanization: a methodological manual to define cities, towns and rural areas for international
21 comparisons: 2021 edition. [WWW Document], n.d. URL <https://data.europa.eu/doi/10.2785/706535>
22 (accessed 3.22.24).
- 23 24. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E,
24 Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for
25 the interpretation of sequence variants: a joint consensus recommendation of the American College of
26 Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.*
27 2015;17(5):405-24.
- 28 25. L'état de santé en France en 2003 - Santé perçue, morbidité déclarée et recours aux soins à travers
29 l'enquête décennale santé | Direction de la recherche, des études, de l'évaluation et des statistiques
30 [Internet]. [WWW Document], n.d. URL [https://drees.solidarites-sante.gouv.fr/publications/etudes-et-
31 resultats/letat-de-sante-en-france-en-2003-sante-percue-morbidite-declaree-0](https://drees.solidarites-sante.gouv.fr/publications/etudes-et-
31 resultats/letat-de-sante-en-france-en-2003-sante-percue-morbidite-declaree-0) (accessed 3.22.24).
- 32 26. Labour force survey | Insee. [WWW Document], n.d. URL
33 <https://www.insee.fr/en/metadonnees/source/serie/s1223> (accessed 3.22.24).
- 34 27. Treiber G, Flaus Furmaniuk A, Guilleux A, Medjane S, Bonfanti O, Schneebeli S, Bernard C, Le-
35 Moullec N, Bakiri F, Pholsena M, Rollot O, Vazier C, Jarlet E, Jéru I, Lascols O, Darcel F, Domun B, Venault
36 A, Venault S, Jacquemont M-L, Doray B, Maiza J-C, Cogne M, Vigouroux C, Nobécourt E. A recurrent familial
37 partial lipodystrophy due to a monoallelic or biallelic LMNA founder variant highlights the multifaceted
38 cardiac manifestations of metabolic laminopathies. *Eur J Endocrinol.* 2021;185(4):453-62.

- 1 28. OFDT Observatoire français des drogues et des toxicomanies, D'Arleux JM, Lermenier-Jeannet A,
2 L'Eprevier AD, ADES JE. 2019 National report (2018 data) to the EMCDDA by the Reitox National Focal Point
3 France. Paris: OFDT; 2019.
- 4 29. Childs GV, Odle AK, MacNicol MC, MacNicol AM. The Importance of Leptin to Reproduction.
5 *Endocrinology*. 2021;162(2):bqaa204.
- 6 30. Dalamaga M, Chou SH, Shields K, Papageorgiou P, Polyzos SA, Mantzoros CS. Leptin at the
7 intersection of neuroendocrinology and metabolism: current evidence and therapeutic perspectives. *Cell*
8 *Metab*. 2013;18(1):29-42.
- 9 31. Schlögl H, Müller K, Horstmann A, Miehle K, Püschel J, Villringer A, Pleger B, Stumvoll M, Fasshauer
10 M. Leptin Substitution in Patients with Lipodystrophy: Neural Correlates for Long-term Success in the
11 Normalization of Eating Behavior. *Diabetes*. 2016;65(8):2179-86.
- 12 32. Schlögl H, Villringer A, Miehle K, Fasshauer M, Stumvoll M, Mueller K. Metreleptin Robustly
13 Increases Resting-state Brain Connectivity in Treatment-naïve Female Patients with Lipodystrophy. *J*
14 *Endocr Soc*. 2023;7(8):bvad072.
- 15 33. Vatier C, Kalbasi D, Vantghem MC, Lascols O, Jéru I, Dagueneil A, Gauthier JF, Buyse M, Vigouroux
16 C. Adherence with metreleptin therapy and health self-perception in patients with lipodystrophic
17 syndromes. *Orphanet J Rare Dis*. 2019;14(1):177.
- 18 34. Vieira DB, Antel J, Peters T, Miehle K, Stumvoll M, Hebebrand J, Schlögl H. Suggestive Evidence for
19 an Antidepressant Effect of Metreleptin Treatment in Patients with Lipodystrophy. *Obes Facts*.
20 2022;15(5):685-93.
- 21 35. Treiber G, Guilleux A, Huynh K, Bonfanti O, Flaus-Furmaniuk A, Couret D, Mellet N, Bernard C, Le-
22 Moullec N, Doray B, Jéru I, Maiza JC, Domun B, Cogne M, Meilhac O, Vigouroux C, Meikle PJ, Nobécourt E.
23 Lipoatrophic diabetes in familial partial lipodystrophy type 2: From insulin resistance to diabetes. *Diabetes*
24 *Metab*. 2023;49(2):101409.
- 25 36. Ali T, Rehman SU, Khan A, Badshah H, Abid NB, Kim MW, Jo HM, Chung SS, Lee HG, Rutten BPF,
26 Kim MO. Adiponectin-mimetic novel nonapeptide rescues aberrant neuronal metabolic-associated
27 memory deficits in Alzheimer's disease. *Mol Neurodegener*. 2021;16(1):23.
- 28 37. He K, Nie L, Ali T, Wang S, Chen X, Liu Z, Li W, Zhang K, Xu J, Liu J, Yu ZJ, Yang X, Li S. Adiponectin
29 alleviated Alzheimer-like pathologies via autophagy-lysosomal activation. *Aging Cell*. 2021;20(12):e13514.
- 30 38. Pasquereau A, Andler R, Guignard R, Soullier N, Beck F, Nguyen-Thanh V. Prevalence of smoking
31 and vaping in France in 2022 among 18-75 years olds. *BEH*. 2023;9-10:152-157
- 32 39. Andler R, Quatremère G, Richard J-B, Beck F, Nguyen-Thanh V. Alcohol use among adults in France
33 in 2021, recent developments and long-term trends. *BEH*. 2024;2:22-31.
- 34 40. Tolonen H, Dobson A, Kulathinal S, WHO MONICA Project. Effect on trend estimates of the
35 difference between survey respondents and non-respondents: results from 27 populations in the WHO
36 MONICA Project. *Eur J Epidemiol*. 2005;20(11):887-98.

1 41. Dossier complet – France | Insee. [WWW Document], n.d. URL
2 <https://www.insee.fr/fr/statistiques/2011101?geo=FRANCE-1#chiffre-cle-5%20> (accessed 3.22.24).

3 42. Les discriminations liées au handicap et à la santé - Insee Première - 1308 [WWW Document], n.d.
4 URL, <https://www.insee.fr/fr/statistiques/1280906> (accessed 3.22.24).

5 43. Dumas A, Allodji R, Fresneau B, Valteau-Couanet D, El-Fayech C, Pacquement H, et al. The right to
6 be forgotten: a change in access to insurance and loans after childhood cancer? J Cancer Surviv Res Pract.
7 2017;11(4):431 7.

8 44. Gomes A, Cook K, Wong A, Tuttle E, Stratton A, Sanders R. Experiences and Perspectives of Patients
9 with Non-HIV-Associated Lipodystrophies and Their Caregivers: A Qualitative Study. The Patient.
10 2021;14(5):673 85.

11

12 **Figure legends**

13 **Figure 1: Depression in patients with genetic lipodystrophy.** A. Distribution of total PHQ-9 score of depression
14 among the cohort of patients with genetic lipodystrophy. The median score is depicted as a horizontal line B.
15 Proportion of patients with genetic lipodystrophy, for each level of depression, according to PHQ-9 questionnaire
16

17 **Figure 2: Distribution of the painful parts of the body in patients with genetic lipodystrophy according to the**
18 **Brief Pain Inventory questionnaire (n=71)**

19 Percentages of the whole group of patients with genetic lipodystrophy answering to the BPI question: “what part(s)
20 of your body are painful?”.

21 **Figure 3: Participants’ responses to the Treatment Burden Questionnaire (n=100)**

22 Percentage of response to each item of the TBQ questionnaire of the whole group of patients with genetic
23 lipodystrophy. The English version of the TBQ questionnaire is composed of 15 items rated on a Likert scale ranging
24 from 0 (not a constraint, percentage of response depicted in white) to 10 (major constraint, percentage of response
25 depicted in black), with percentages of responses ranging from 1 to 9 sequentially depicted in grey. The TBQ
26 questionnaire assesses the burden associated with taking medicine as a reminder of chronic condition, following
27 advice of dietary changes, doctor appointments, advice of physical activity recommendations, appointment planning,
28 laboratory tests and other exams, effort to remember to take medication, administrative tasks, financial constraints,
29 self-monitoring, relationship with healthcare professionals, medication intake frequency, specific conditions of
30 medication intake, galenic form and social impact of the treatment. The mean score \pm standard deviation for each
31 item is depicted at the right side of the figure.

32 **Figure 4: Body Image in women with genetic lipodystrophy.** A. Percentages of responses to Body Image Scale
33 questionnaire of women with genetic lipodystrophy (n= 84). B. Body parts for which women CGL (n=10) reported
34 dissatisfaction. C. Body parts for which women with FPLD (n=64) reported dissatisfaction

35 Percentages of responses to each item of the Body Image Scale (BIS) questionnaire of women with genetic
36 lipodystrophy, depicted in white (“not at all”, score 0), grey (“slightly”, score 1, or “moderately”, score 2), or black
37 (“very much”, score 3)

38

39

1 **Table 1: Sociodemographic and clinical characteristics of the overall population of patients with genetic**
 2 **lipodystrophy**

	Total, N=109		Familial partial lipodystrophy (FPLD), N=93		Congenital generalized lipodystrophy (CGL), N=16		p (FPLD vs CGL)
	n	%	n	%	n	%	
Socio-demographic factors							
Gender N=109							0.36
Women	92	84	80	86	12	75	
Men	17	16	13	14	4	25	
Age (years) N=106							0.04
18-44	55	52	43	48	12	75	
45-64	36	34	35	39	1	6	
65-74	11	10	9	10	2	13	
≥ 75	4	4	3	3	1	6	
Birthplace N=108							0.07
Metropolitan France	67	62	55	60	12	75	
Overseas territories	29	27	28	30	1	6	
Other	12	11	9	10	3	19	
Location of current residency N=100							0.003
Rural	14	14	11	13	3	19	
Small urban area	56	56	53	63	3	19	
Large urban area	30	30	20	24	10	62	
Location of residency in adolescence N=95							0.06
Rural	15	16	13	16	2	15	
Small urban area	48	50	45	55	3	23	
Large urban area	32	34	24	29	8	62	
Educational level of patients N=106							0.45
Low	40	38	36	40	4	27	
Intermediate	37	35	32	35	5	33	
High	29	27	23	25	6	40	
Occupational category of patients N=98							0.14
Low	23	24	17	20	6	43	
Intermediate	56	57	51	61	5	36	
High	19	20	16	19	3	21	
Clinical factors							
Current BMI (kg/m ²) N=102	24 (23-27)	NA	25 (23-28)	NA	23 (19-25)	NA	0.02
Age at diagnosis of lipodystrophy (years) N=94	30 (23-47)	NA	33 (24-47)	NA	10 (1-25)	NA	<0.0001
Smoking status N=102	41	40	37	42	4	29	0.33
Regular (weekly) alcohol consumption N=102	20	20	18	21	2	14	0.73
	51	49	44	49	7	50	0.97

1 Notes: Results are expressed as percentage (%; italic values) for qualitative variables, or as median (25^e-75^e
 2 percentile) for quantitative variables. Results are from all patients unless specified (N). P values are obtained from
 3 unpaired Mann-Whitney U-test for quantitative variables and from chi-squared tests for qualitative variables. BMI:
 4 body mass index. CGL: congenital generalized lipodystrophy. FPLD: familial partial lipodystrophy. NA: non available.

5

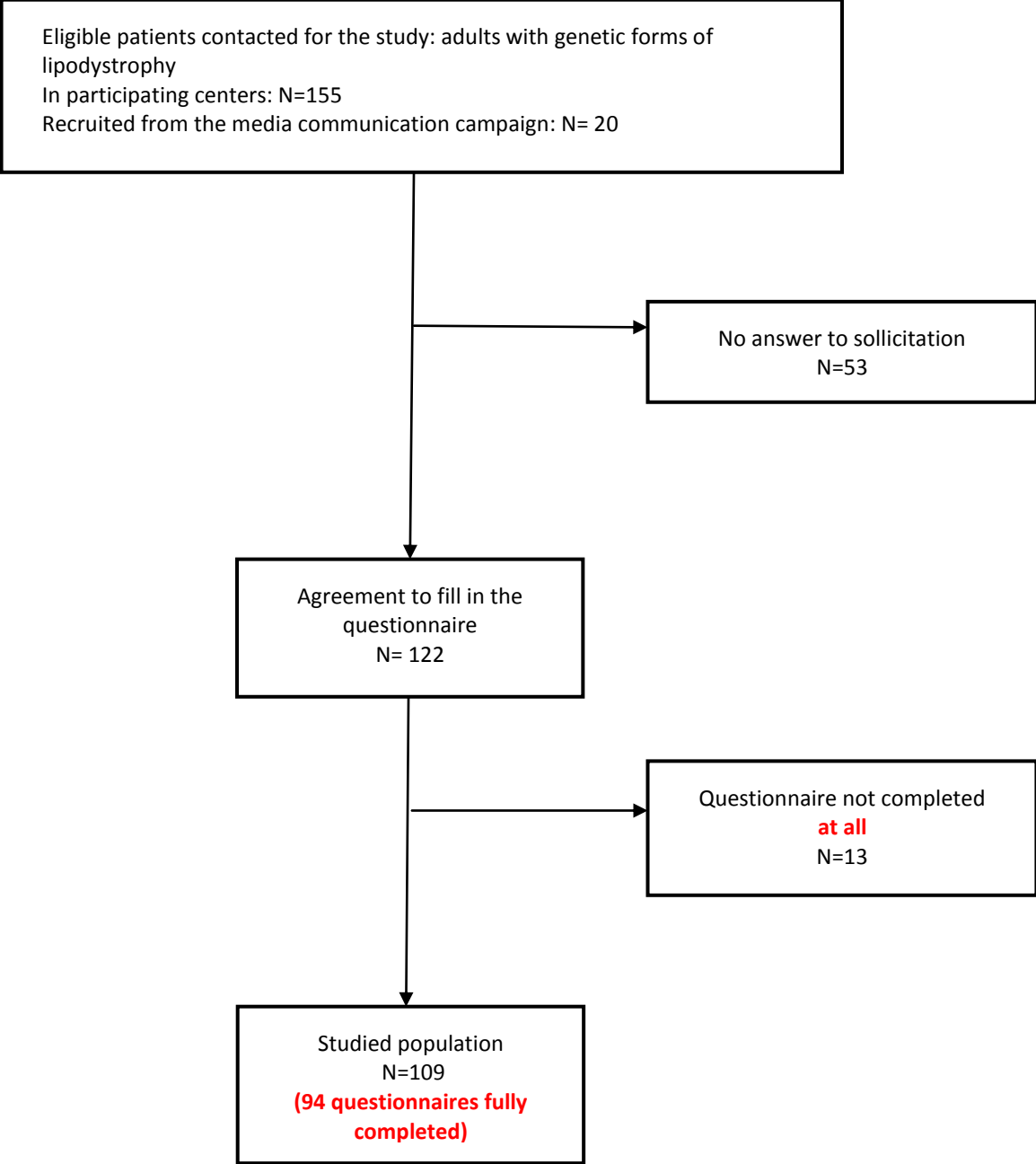
6 **Table 2: Health-Related Quality of Life measured with SF-12 questionnaire, according to gender**

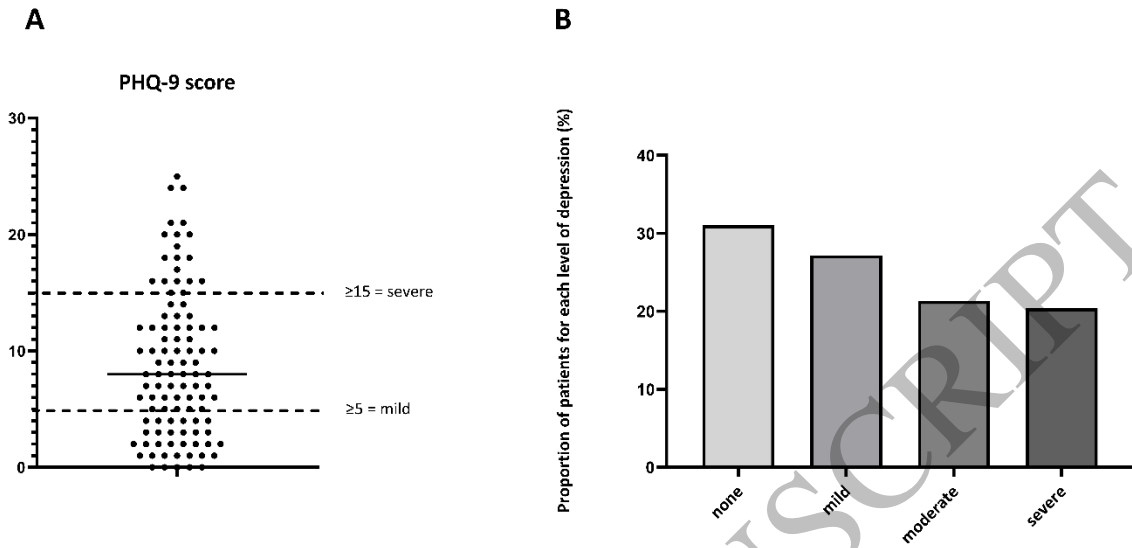
	Mean score in LDG cohort of female (n=90)	Mean score in French female general population	p (female, LDG cohort vs French population)	Mean score in LDG cohort of male (n=16)	Mean score in French male general population	p (male, LDG cohort vs French population)	p (female vs. male in LDG cohort)
PCS	44.06 (10.14)	49.95 (10.26)	<0.001	46.57 (7.65)	50.91 (9.47)	0.038	0.348
PF	64.33 (31.92)	82.11 (24.19)	<0.001	71.67 (32.55)	86.28 (22.38)	0.104	0.416
RP	61.72 (26.29)	79.18 (34.43)	<0.001	74.37 (27.80)	82.71 (32.07)	0.249	0.083
BP	59.83 (33.0)	69.75 (25.50)	0.006	71.87 (28.69)	75.02 (24.26)	0.667	0.174
GH	38.48 (20.66)	66.58 (19.17)	<0.001	40.62 (17.97)	68.48 (18.76)	<0.001	0.698
MCS	39.53 (12.16)	45.57 (10.35)	<0.001	48.11 (10.76)	50.25 (9.27)	0.438	0.010
VT	31.95 (22.41)	54.82 (18.32)	<0.001	48.57 (27.97)	59.70 (17.64)	0.160	0.015
SF	53.09 (27.39)	78.10 (22.25)	<0.001	78.12 (30.10)	82.95 (20.79)	0.531	0.001
RE	57.33 (28.96)	78.34 (35.32)	<0.001	71.33 (34.82)	84.29 (31.33)	0.172	0.097
MH	49.2 (21.67)	63.76 (18.33)	<0.001	63.75 (23.34)	69.39 (16.75)	0.349	0.016

7 Health Related Quality of Life (HRQoL) was assessed using the French version of the Short Form-12 Health Survey
 8 (SF-12) (14), a generic health status measurement instrument, which gives two health summary scores, the Physical
 9 Component Summary (PCS) and the Mental Component Summary (MCS), as well as its 8 sub-dimensions: Physical
 10 Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH) for PCS; ViTality (VT), Social Functioning
 11 (SF), Role Emotional (RE), and Mental Health (MH) for MCS. A higher score corresponds to a better quality of life.
 12 Raw mean scores were compared to the mean scores of the general French population, using data from the latest
 13 French national 10-year health survey, according to gender (24). Scores were compared between males and females.
 14 P values are obtained from unpaired Mann-Whitney U-test.

15

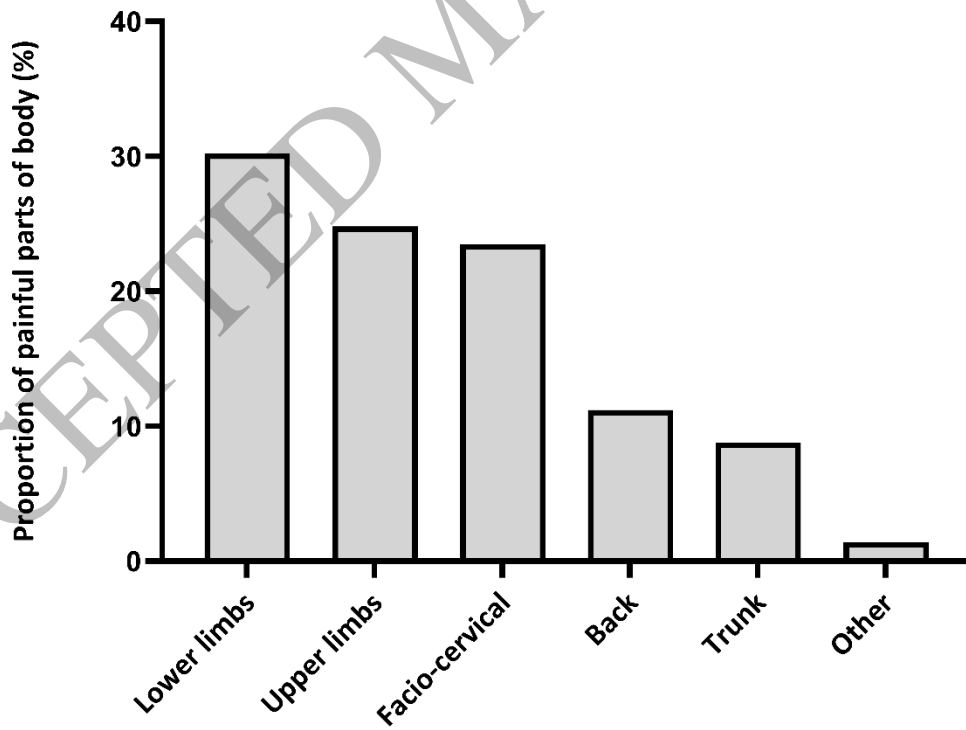
Supplemental Figure 1 : Flow chart of the study





1
2
3

Figure 1
160x83 mm (x DPI)



4
5
6

Figure 2
141x118 mm (x DPI)

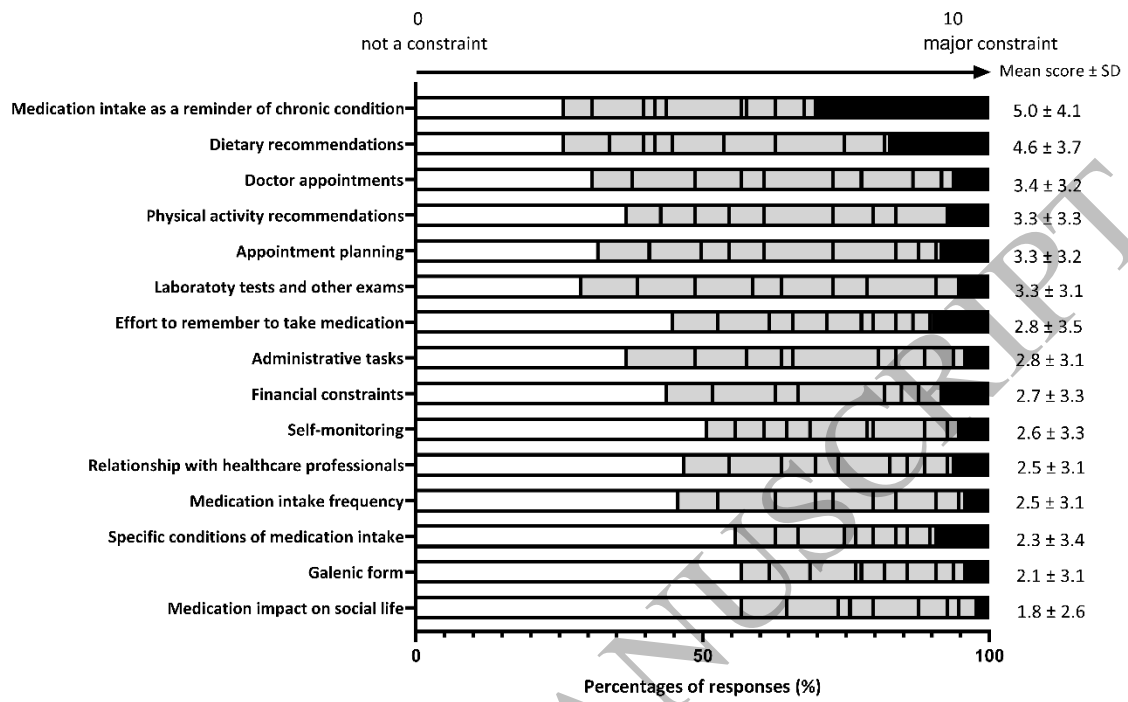


Figure 3
160x101 mm (x DPI)

1
2
3

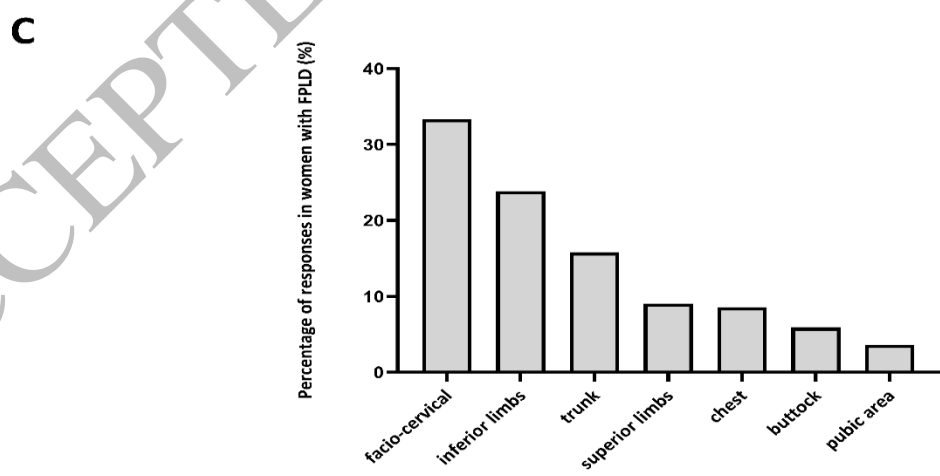
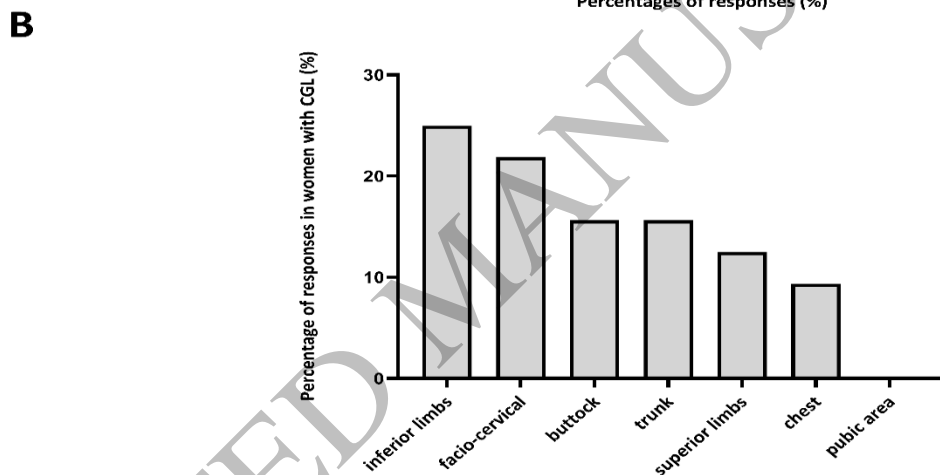
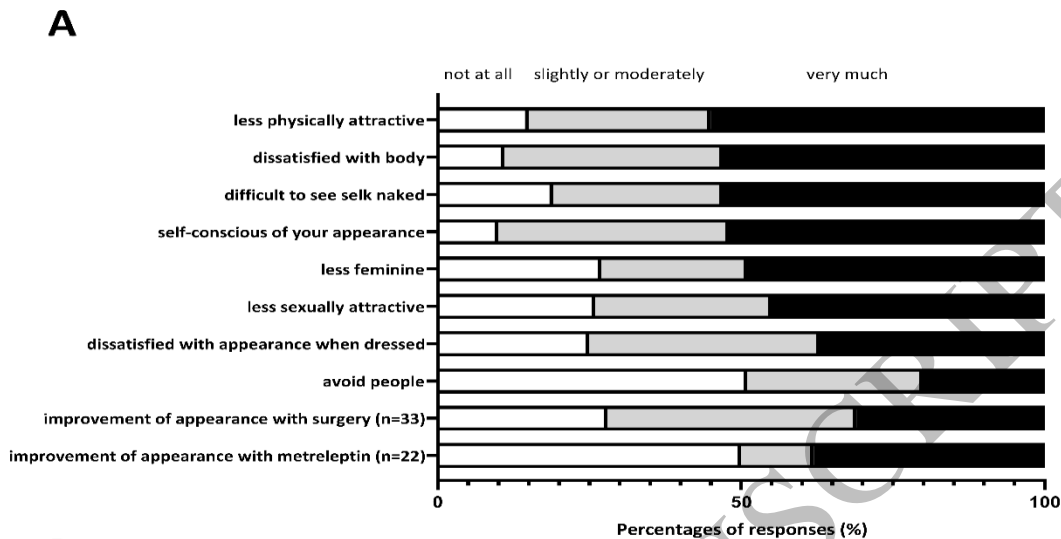


Figure 4
158x247 mm (x DPI)

1
2
3