Health-related quality of life in multiple musculoskeletal conditions: a cross-sectional population based epidemiological study. II. The MAPPING study

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Abstract

Objective
Musculoskeletal conditions are a major burden on individuals, health systems, and social care systems. The objective of the MAPPING study was to assess the impact of musculoskeletal conditions on health-related quality of life (HRQL) in an Italian population sample.

Methods
Trained rheumatologists carried out structured visits in which subjects were asked about musculoskeletal symptoms and socio-demographic characteristics, completed validated instruments for measuring HRQL, such as the Short Form 36 items status survey questionnaire (SF-36), the EUROQoL five item questionnaire (EQ-5D), and chronic pain severity (Chronic Pain Grade - CPG questionnaire), and underwent a standardized physical examination. We considered a sample size of 576 patients diagnosed as having had musculoskeletal conditions. For the purposes of this study, musculoskeletal diseases were classified into 4 diagnostic groups: inflammatory rheumatic diseases (IRD), symptomatic peripheral osteoarthritis (SPOA), low back pain (LBP), and soft tissue disorders (STD). Cases were defined by previously validated criteria.

Results
The 4 major musculoskeletal disease groups, compared to non-sufferers, significantly impaired all eight health concepts of the SF-36 in the following order of magnitude: IRD, SPOA, STD, and LBP. Similar results were found for EQ-5D. The most striking impact was seen for SF-36 physical measures. On multiple regression modelling the physical component (PCS) of the SF-36 was influenced by female sex, age, high BMI, and low educational level (all at a p level < 0.001), and by manual occupation (p = 0.028) and chronic co-morbidity (p = 0.035) in LBP. In SPOA, factors influencing physical function were age (p = 0.0001), low educational level (p = 0.006), female sex (p = 0.028), and chronic co-morbidity (p = 0.037). Moreover, an association on chronic co-morbidity and low educational level (both at a p level < 0.001), age (p = 0.0004), and manual occupation (p = 0.035) was found with IRD, as well as of chronic co-morbidity and low educational level (both at a p level < 0.001), female sex (p = 0.006) and high BMI (p = 0.036) with STD were also found. Similar results were found for EQ-5D.

Conclusions
The MAPPING study indicates that musculoskeletal conditions have a clearly detrimental effect on the HRQL and one third of the adult population in Italy visited at least one physician for musculoskeletal problem in the past year. These results enable a comparison to be made of the burden of musculoskeletal conditions with that of other common chronic conditions.

Key words
Musculoskeletal conditions, health-related quality of life, pain, disability, health survey.

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*Members of the MAPPING study are shown in the appendix.

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Introduction
The Bone and Joint Decade 2000-2010 has been established to increase awareness of the impact of musculoskeletal conditions on the individual, the health care system and society (1). To describe the global burden of musculoskeletal diseases now and in the future is a central goal of the decade (1). Comparative studies on the impact of musculoskeletal conditions across countries can help to provide an understanding of country-specific factors contributing to the burden of disease and can help to target the patients’ needs specifically (2, 3). However, few studies have been performed in the past decade and many of those available have methodological shortcomings (4-9). In addition, the organization and quality of healthcare provided to patients can influence the disease severity, and socioeconomic characteristics can influence the perceived health status (10-12).

Increasingly, health status is being measured using health-related quality of life (HRQL) instruments (13). HRQL is a multi-domain construct that refers to those aspects of human life and activities that are generally affected by health conditions or health services (14), although, in the case of disease, almost all aspects of life can become health related (15). Specific examples of HRQL domains include pain, functional status, psychological distress, fatigue, and other key patient symptoms (16). The Medical Outcomes Study Short Form 36 (SF-36) items status survey questionnaire (17) and the EUROQoL five item questionnaire (EQ-5D) for measuring HRQL (18, 19) are emerged as being the most widely used generic instruments for measuring perceived health status in various diseases and conditions, and has also been suggested to be the most appropriate generic instrument for use in musculoskeletal conditions. The SF-36 has been translated and validated in several countries including Italian (20), and has been found to be a valid measure of change in population health (21-23). These instruments have been shown acceptable psychometric properties in patients with rheumatoid arthritis (RA) (21-30) osteoarthritis (OA) (31-35), chronic back disorders (36, 37), chronic widespread pain and fibromyalgia (38-41) and has been used as HRQL measure in clinical studies in a variety of musculoskeletal conditions (42-45). Most of these studies focused on only one musculoskeletal disease, but co-morbidity of musculoskeletal conditions is common. In addition, comparison between studies is often limited owing to differences in study design, case definition and selection, age group, presentation of the data, and probably also language and culture. Data on HRQL in patients with different musculoskeletal conditions should preferably be based on a single large dataset and should take into account the coexistence of musculoskeletal diseases. In this paper we present data on HRQL (using both SF-36 and EQ-5D) for different musculoskeletal conditions as assessed in a population-based survey in Italy.

Patients and methods
Sample and data collection procedures
We considered a sample size of 576 patients diagnosed as having had musculoskeletal conditions. For the purposes of this study, musculoskeletal conditions were classified into 4 diagnostic groups: inflammatory rheumatic diseases (IRD), symptomatic peripheral osteoarthritis (SPOA), low back pain (LBP), and soft tissue disorders (STD). At the time of HRQL assessment, patients underwent complete clinical and laboratory investigations. The methods used for definitions and case identification made on the basis of the American College of Rheumatology (ACR, formerly the American Rheumatism Association) criteria (46-53), the criteria of other international study groups (54, 55), or internationally used criteria (56-63) have been detailed elsewhere (64) (Table I).

In all patients, the presence of co-morbidities was also assessed. These were ascertained through patient’s self-reports using additional questions probed for the presence of nine specific co-morbid conditions (hypertension, myocardial infarction, lower extremity arterial disease, major neurological
problem, diabetes, gastrointestinal disease, chronic respiratory disease, kidney disease, and poor vision). The algebraic sum of positive responses was calculated for each subject, giving a comorbidity factor with a possible range from 0 to 9. Moreover, HRQL assessment was performed in a group of 1579 healthy subjects as controls. These subjects had also participated in the survey about the occurrence of musculoskeletal pain, details of which are given in the part I of the Mapping study (64). The medical ethics committee approved the study and all patients gave their written consent.

Questionnaires
The questionnaire sought socio-demographic data (age, gender, education, employment status, occupation, body mass index-BMI), information on musculoskeletal pain, and a validated instrument for assessing chronic pain severity and HRQL. Age is given in years. Educational level was separated into three categories based on the Italian school system: 1 = primary school, 2 = secondary school, and, 3 = high school or university. The BMI was derived from the self-reported height and weight (body weight divided by the square of the height).

Chronic pain assessment. Chronic pain severity was assessed using the Chronic Pain Grade (CPG) questionnaire (65). The CPG consists of the following seven items. Current pain intensity, worst pain intensity, and average pain intensity in the past six months were assessed by three items using an 11-point rating scale (0 = "no pain", 10 = "pain as bad as could be"). One item assessed the number of days during that period that the respondent has been kept from his/her usual activities (work, school or housework). The remaining three items assessed disability in the past six months. The extent of interfer-
ence with daily activities, the ability to take part in recreational, social and family activities, and the ability to work (including housework) was assessed using an 11-point rating scale (0 = "no interference", 10 = "unable to carry on any activities"). The questionnaire classifies chronic pain into four hierarchical grades: Grade I (low disability - low intensity), Grade II (low disability - high intensity), Grade III (high disability - moderately limiting), and Grade IV (high disability - severely limiting) (65). The CPG is valid and reliable for use as a self-completion postal questionnaire in the general population (66). The HRQL in multiple musculoskeletal conditions / F. Salaffi et al.

The EQ-5D is a standardised, self-administered questionnaire that classifies the patient into one of 243 health states (18, 19). It describes HRQL in terms of five dimensions: mobility, self-care, usual activities (work, study, housework, family or leisure), pain/discomfort, and anxiety/depression. Each dimension is subdivided into three levels indicating no problem, a moderate problem or an extreme problem. A five-digit code number relating to the relevant level of each dimension can describe different health states. A perception of "own health state" VAS is also part of the EQ-5D but is scored separately. The anchors for this graduated scale are represented in three distinct forms; Part 1 may be presented either as a profile (EQ-5D profile), based on the unweighted responses indicating a patient’s level of problem in each of the five domains, or as a health index (EQ-5D index), by applying a suitable weighting system such as the utilities obtained from the UK national survey (18, 19, 69). Utility scores range from -0.59 to 1.00, with 0 being dead and 1.00 the state of full health. The VAS rating in Part 1 can be interpreted directly as a quantitative measure of the patient’s valuation of their own global health status (EQ-5Dvasc). EQ-5D is self-completed by respondents and ideally suited for use in postal surveys, clinics and face-to-face interviews. The EQ-5D index and EQ-5Dvasc scores were used in this study. The validity and reliability of the EQ-5D have been found acceptable in Europe among different populations and patient groups (69, 70). Despite the limited number of dimensions and levels, the instrument has been found to be sensitive to improvements in HRQL (71).

Statistical analysis
Excel (Microsoft), SPSS (version 11.0), and MedCalc® software (version 7.4.2.0) for Windows XP, were used to perform all analyses. Mann-Whitney non-parametric analysis was used to compare mean values. The Spearman’s correlation coefficient was used to evaluate the relationship between pain measures and the mental component of SF-36. A probability value of ρ < 0.05 was considered significant; 95% confidence intervals (CI) were given where relevant.

A chi-square analysis was also used to evaluate for differences in demographic characteristics and various health and illness variables between persons with musculoskeletal diseases and those without musculoskeletal diseases. A variety of factors shown by chi-square detection to be significantly associated with poor HRQL in major rheumatic groups were identified for further analysis: age (as a continuous variable); sex (as a dichotomous variable); 0 = male; 1 = female); BMI (as a continuous variable); educational level (years of education as a continuous variable); and manual or non-manual occupation (as a dichotomous variable: 1 = manual occupation; 0 = non-manual occupation), and reported co-morbid conditions. All these factors were then introduced as covariates in multiple regression models in which SF-36 PCS and EQ-5D score were dependent variables. Variables were entered simultaneously.

Results
Demographics
576 patients (358 females, 218 males) with musculoskeletal conditions, classified into 4 diagnostic groups, were studied: IRD (N = 66 patients), SPOA (N = 193 patients), LBP (N = 127 patients), and STD (N = 190 patients). The mean age of the group with musculoskeletal conditions was 61.5 ± 13.5 yr. The mean age of the control group of 1579 healthy subjects was 55.2 ± 19.2 yr, with a significant difference (p < 0.001). In total, we found that 30.1% of the subjects in the sample (576 patients diagnosed as having had musculoskeletal conditions plus 1579 healthy controls) had visited a physician for musculoskeletal problems in the past year. Extrapolating the Italian’s adult population, more than 14 million people consult a physician with a problem related to the musculoskeletal system annually.
Severity of pain and health-related quality of life

The percentage of patients reporting severe chronic pain (grade III and IV) on CPG questionnaire, resulting in high disability, was highest for IRD (22.7%), intermediate for LBP (12.6%), and lowest for SPOA and STD (10.4% and 9.5%, respectively) (Fig. 1). There were significant differences in the distribution of grades of pain between men and women (p < 0.005), and the frequency of the more severe pain grades increased with age (p < 0.001).

Table II provides statistics summarizing the mean, standard deviation, and 95% confidence intervals for the mean for each of the aspects of health status covered by the SF-36 and EQ-5D for the different diagnostic groups and controls. Mann-Whitney non-parametric analysis was performed to test for differences. The 4 major rheumatic disease groups, compared to non-sufferers, significantly impaired all eight health concepts of the SF-36 in the following order of magnitude: IRD, SPOA, STD, and LBP. Similar results were found for EQ-5D (Table II). The most striking impact was seen for SF-36 physical measures "physical role" and "physical functioning", as well as "bodily pain" (Fig. 2). Women and older age adults tended to report lower SF-36 scores. For the SF-36 and EQ-5D, we have strong evidence that the mean (95% CI for mean) of the scores differ significantly between the CPG groups (p < 0.0001) (Fig. 3). We also investigated the relationship between pain scores with SF-36 MCS in all suffering patients. The SF-36 health concept Bodily Pain and pain intensity of the CPG questionnaire correlated well both at a p < 0.0001 (Table II). We also investigated the relationship between pain scores with SF-36 PCS in all suffering patients. The SF-36 health concept Bodily Pain and pain intensity of the CPG questionnaire correlated well both at a p < 0.0001.

Table II. Descriptive statistics and features of HRQL score distributions for patients with musculoskeletal disorders (no. of patients = 576) and healthy controls (no. of subjects = 1579).

<table>
<thead>
<tr>
<th>SF-36 subscales</th>
<th>IRD (n = 66)</th>
<th>SPOA (n = 193)</th>
<th>LBP (n = 127)</th>
<th>STD (n = 190)</th>
<th>Controls (n = 1579)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 PCS (mean=50;SD=10)</td>
<td>35.8 (8.8)</td>
<td>33.8 (13.1)</td>
<td>40.1 (9.8)</td>
<td>40.0 (8.4)</td>
<td>38.5 (4.1)</td>
</tr>
<tr>
<td>SF-36 MCS (mean=50;SD=10)</td>
<td>41.3 (10.0)</td>
<td>38.7 (14.3)</td>
<td>41.4 (10.6)</td>
<td>41.5 (10.7)</td>
<td>45.4 (9.4)</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>55.4 (24.7)</td>
<td>51.7 (23.8)</td>
<td>65.6 (24.5)</td>
<td>67.8 (23.3)</td>
<td>82.5 (20.7)</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>45.2 (20.9)</td>
<td>47.9 (18.9)</td>
<td>46.5 (17.5)</td>
<td>48.1 (17.5)</td>
<td>56.8 (15.4)</td>
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PCS: Physical Component Summary scale score; MCS: Mental Component Summary scale score; EQ-5D: European Quality of Life Questionnaire.

Significances were tested using non-parametric Mann-Whitney U test: *Significantly different from healthy controls at p < 0.01; †significantly different from healthy controls at p < 0.001; ‡ significantly different from healthy controls at p < 0.0001.

Risk factors associated with poor health-related quality of life

To test the association between the musculoskeletal conditions and the SF-36 PCS scores, we first studied the bivariate effect of different variables on these scores. The factors associated with worse SF-36 PCS scores, we first studied the range of conditions. The factors associated with worse SF-36 PCS scores, we first studied the range of conditions. The factors associated with worse SF-36 PCS scores, we first studied the range of conditions.

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al level \( p < 0.005 \), high BMI \( p < 0.008 \), manual occupation \( p < 0.03 \), and having a diagnosis of co-morbid conditions \( p < 0.001 \). All these factors were introduced as covariates in a multiple regression model in which SF-36 PCS score was dependent variable. The physical component (PCS) of the SF-36 was influenced by female sex, age, high BMI, and low educational level (all at a \( p \) level \( < 0.001 \)), and by manual occupation \( p = 0.028 \) and chronic co-morbidity \( p = 0.035 \) in LBP. In SPOA, factors influencing physical function were age \( p = 0.0001 \), low educational level \( p = 0.006 \), female sex \( p = 0.028 \), and chronic co-morbidity \( p = 0.037 \). Moreover, an association on chronic co-morbidity and low educational level (both at a \( p \) level \( < 0.001 \)), age \( p = 0.004 \), and manual occupation \( p = 0.035 \) was found with IRD, as well as of chronic co-morbidity and low educational level (both at a \( p \) level \( < 0.001 \)), female sex \( p = 0.006 \) and high BMI \( p = 0.036 \) with STD were also found (Table III).

With regard to the mental component (SF-36 MCS), no association were found with age, high BMI, manual occupation and with low educational level, and the only significant associations appeared to be with female sex \( p < 0.01 \) and with a diagnosis of any chronic diseases \( p < 0.005 \) in SPOA and LBP. Concerning the EQ-5D, it was influenced by female sex, age, (both at a \( p \) level \( < 0.001 \)), and chronic co-morbidity and low educational level (both at a \( p \) level \( < 0.001 \)) in LBP, and by a chronic co-morbidity and low educational level (both at a \( p \) level \( < 0.01 \)) in IRD were found.

Discussion

To the best of our knowledge, this is the first time that the burden of musculoskeletal conditions in adults, in terms of impact on HRQL have been described in a general sample of the Italian adult population. HRQL is not only a primary concern of patients, their families, and clinicians, but is also of policy interest. Estimates of the relative im-
Table III. Factors influencing physical function (SF-36 PCS); a multiple regression models.

| IRD: Sample size 66 patients (regression equation) |  |
|----------------------------------|-----------------|-----------------|-----------------|
| Independent variables            | Coefficient     | Std. error      | t       | p      |
| Age                              | -1.6202        | 0.02588         | 3.016   | 0.0038 |
| Malignant occupation             | 0.19017        | 0.05072         | 3.855   | 0.0008 |
| Educational level                | -0.70600       | 0.20233         | -3.393  | 0.0009 |
| F ratio                          | 35.2778        | p < 0.0001      |        |       |

| LBP: Sample size 127 patients (regression equation) |  |
|----------------------------------|-----------------|-----------------|-----------------|
| Independent variables            | Coefficient     | Std. error      | t       | p      |
| Age                              | -1.69400        | 0.02588         | 3.123   | 0.0015 |
| Malignant occupation             | 0.13917        | 0.05072         | 2.765   | 0.0063 |
| Educational level                | -0.70600       | 0.20233         | -3.403  | 0.0009 |
| F ratio                          | 48.0484        | p < 0.0001      |        |       |

| SPOA: Sample size 193 patients (regression equation) |  |
|----------------------------------|-----------------|-----------------|-----------------|
| Independent variables            | Coefficient     | Std. error      | t       | p      |
| Age                              | -1.58129        | 0.03586         | 4.403   | 0.0001 |
| Educational level                | -0.20828       | 0.07572         | -2.765  | 0.0063 |
| Female sex                       | 0.30643        | 0.20541         | 3.982   | 0.0028 |
| Co-morbidity                     | -0.02314       | 0.05747         | -0.106  | 0.0377 |
| F ratio                          | 48.0484        | p < 0.0001      |        |       |

| STD: Sample size 199 patients (regression equation) |  |
|----------------------------------|-----------------|-----------------|-----------------|
| Independent variables            | Coefficient     | Std. error      | t       | p      |
| Age                              | -1.58129        | 0.03586         | 4.403   | 0.0001 |
| Educational level                | -0.20828       | 0.07572         | -2.765  | 0.0063 |
| Female sex                       | 0.30643        | 0.20541         | 3.982   | 0.0028 |
| Co-morbidity                     | -0.02314       | 0.05747         | -0.106  | 0.0377 |
| F ratio                          | 48.0484        | p < 0.0001      |        |       |

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The impact of chronic diseases on HRQL is needed to better plan and allocate resources for research, training, and health care.

The strength of our study is the assessment of multiple musculoskeletal conditions. The study confirms the severe multidimensional impact on HRQL reported in patients with musculoskeletal conditions, typically in the areas of pain, physical functioning or mobility, role limitation due to physical health problems, and usual activities (72-78). The worst quality of life patterns were found for IRD and LBP. The results were similar for both SF-36 and EQ-5D. In addition, the percentage of patients reporting severe chronic pain (CPG grade III or IV), resulting in high disability, was highest for IRD (22.7%), intermediate for LBP (12.6%), and lowest for SPOA and STD (10.4% and 9.5%), respectively. The results show that there are differences in scores between individuals according to their CPG in both summary scale score measured by the SF-36. As the grade increases from I to IV, mean scores on the SF-36 physical and mental dimension become progressively lower. This confirms the widespread impact of chronic musculoskeletal pain on all aspects of health, and supports the multidimensional view. Other studies have also shown that chronic musculoskeletal pain has severe impact on health status measured with SF-36 (40, 79, 80). The impact on the different health concepts has been reported to vary in regional pain syndromes, depending on location. Birrell et al. (81) found that hip pain had impact on physical function and pain, but only a small impact on wider aspects of health status, such as general health, vitality and mental health. Specifically, musculoskeletal diseases are associated with some of the poorest quality-of-life issues, particularly in terms of physical functioning, role functioning and bodily pain, were quality of life is lower than for gastrointestinal disorders, urogenital conditions, psychiatric disorders, chronic respiratory diseases, cerebrovascular/neurologic conditions, and cardiovascular conditions (28, 82-87). Our findings are also consistent with those found by Becker et al. (79) in chronic non-malignant pain (such as facial, thoracic, or rectal) patients referred to a multidisciplinary pain centre. This has important implications for the quantity and type of healthcare needed. Our findings that one out of three physician office visits was made for musculoskeletal conditions is similar to data (27%) found over a 2-week period in Finland (88) or that (29.7%) observed over a 1-yr period in the USA (89). Apart from the higher prevalence in women for nearly all of the rheumatic conditions analysed (with the exception of SpA and gout) (64), we also found that women had poorer HRQL than men in all dimensions of SF-36. These findings are consistent with those of previous reports (77, 90). In a Spanish epidemiological study, the SF-12 - a shortened version of SF-36 - was used to measure HRQL of adults with pain problems (73). The study found that persons reporting RA, LBP and OA of the knee scored lower on the SF-36 PCS but not on the SF-36 MCS (73). In a study carried out in Scotland analysing the impact on chronic pain in the community, it was found that chronic musculoskeletal pain was associated with poor health in all dimensions of SF-36 (91). Similar to the Scottish study (91), we found that chronic pain was associated with a decrease in health in all of the dimensions of SF-36. We also observed, in agreement with the Spanish study (73), that the
physical dimensions of the SF-36 were more strongly affected by pain than the psychological dimensions. Epidemiological studies have reported that apart from the gender difference there are other differences in the distribution of chronic musculoskeletal pain in the population. Several studies have found that socio-economic factors such as low education and psychological factors are associated with chronic pain-associated disability (75, 77, 92, 93). Years of formal education have been reported to be a risk factor for presence of chronic musculoskeletal pain and physical function in the community (92, 94). In outpatients with SPOA, Callahan et al. (94) found education to be related to pain severity as measured by a simple visual analogue scale. Previously, we found education to be related to physical function and pain as measured by Arthritis Impact Measurement Scales (AIMS2) (95) and Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (34, 35). Our present data shows that a low educational level was not a risk factor of LBP and SPOA disability. This is in line with the results of previous studies (65, 91, 96). The mechanism by which education influences pain disability or psychological process is unclear but may be related to enhanced self-efficacy and sense of control allowing the patient to take advantage of a greater number of pain reducing modalities. Co-morbidity between musculoskeletal conditions as well as other medical problems has been discussed (75, 82). Several studies, using data from the National Health Interview Survey Supplement on Aging (97) and Longitudinal Supplement on Aging (98), the Framingham Study (99), the Ontario Health Survey (90), and the Women’s Health and Aging Study (100) have demonstrated the role of co-morbidities in the relationship between OA and disability. There is a growing amount of evidence to suggest that musculoskeletal pain-associated disability and psychological variables such as anxiety and depression may be an indicator for more severe pain behaviour, which has a central role in the chronic pain-processes (101, 102). In this study we didn’t tried to examine these other components, but the high degree of interrelationship between pain scores (SF-36 bodily pain and CPG - pain intensity) and the SF-36 MCS, strongly supports the concept that pain intensity is a major component of the patient’s global health response. As age, sex, educational level, occupation, and other chronic diseases were likely to be confounders, we controlled for these factors in the analyses as described above. A possible problem with this study was a selection bias due to non-response. This non-response might have exerted a differential bias across conditions. For example, one could imagine that persons with severe levels of musculoskeletal pain or disability are expected to be more motivated to complete a lengthy questionnaire than with mild levels of disease (103, 104). Second, in a number of data sets the selection of patients was limited with respect to socio-demographic characteristics. Third, the representativeness may also have been affected adversely by limited sample size. Finally, the number of sub-samples per condition varies considerably. Clearly, the larger the number of sub-samples the more likely the combination of samples will provide a representative picture of the particular disease. Despite these limitations, the data are expected to provide a realistic representation of these musculoskeletal conditions in the Italy, given the diversity and magnitude of the eight data sets, the face validity of the results, and the concordance with results from the literature.

In conclusion, this inception investigation demonstrates that the musculoskeletal conditions have a clearly detrimental effect on the HRQL and one third of the adult population in Italy visited at least one physician for musculoskeletal problem in the past year. This observation is in line with previous studies (73, 88, 89, 105). The physical domain is predominantly affected, but mental and social function are also impaired in comparison with control group findings. The SF-36 and the EQ-5D may be used as generic instruments to measure HRQL; they performed equally well in assessing HRQL in patients with musculoskeletal conditions. Longitudinal studies are required to identify factors associated with poor HRQL.

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Appendix

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