2019

Symptom profile of patients receiving antibiotics for upper respiratory tract infections in general practice: An observational study using smartphone technology

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This article was originally published as:
Jiwa, M., Krejany, C., Kanjo, E., Leeb, A., & Peters, I. J. (2019). Symptom profile of patients receiving antibiotics for upper respiratory tract infections in general practice: An observational study using smartphone technology. *Family Practice, Early View (Online First)*.

Original article available here:
10.1093/fampra/cmy134

Symptom profile of patients receiving antibiotics for upper respiratory tract infections in general practice: an observational study using smartphone technology.

Running Head (short title) Symptom profile of patients receiving antibiotics for URTI

Article Category Epidemiology

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Key messages

- Antibiotics are prescribed at higher than recommended rates for URTI
- We describe URTI patients' symptom trajectory after antibiotic prescription
- Patients prescribed antibiotics did not experience reduced symptom severity
- Patients prescribed antibiotics did not recover faster
- The survey was conducted using smartphone technology in real-time

Abstract

Background Upper respiratory tract infections (URTI) are a common presentation in general practice and are linked to high rates of inappropriate antibiotic prescription. There is limited information about the trajectory of patients with this condition who have been prescribed antibiotics.

Objectives To document the symptom profile of patients receiving antibiotics for URTIs in Australian general practice using smartphone technology and on-line surveys.

Methods 8218 patients receiving antibiotics after attending one of 32 general practice clinics in Australia from June to October 2017. 4089 were identified as URTI presentations and were the cohort studied. Patients completed the Wisconsin Upper Respiratory Symptom Survey (WURSS-24) 3 and 7 days after visiting their GP.

Results 614 URTI-specific patients responded to at least one symptom survey (RR 15%). The majority of patients reported moderate to mild symptoms at 72 hours [median global symptom severity score 37 (IQR 19, 59)] post GP visit which reduced to very mild symptoms or not sick by day 7 [11 (IQR 4,27)]. Patients receiving antibiotics for URTI reported the same level of symptom severity as patients in previous studies receiving no treatment.

Conclusions The recovery of most patients within days of receiving antibiotics for URTI mimics the trajectory of patients with viral URTIs without treatment. Antibiotics did not appear to hasten recovery. Monitoring of patients in this context using smart phone technology is feasible but limited by modest response rates.

Keywords

antibiotics, antimicrobial stewardship, infectious diseases, primary care, respiratory diseases, upper respiratory infections

Introduction

As in many other countries world-wide people in Australia who are worried about their symptoms are able to consult a general practitioner (GP). The GP service is subsidised by the government and many doctors do not charge above the government subsidy. Upper respiratory tract infections (URTI) are the most common new problem presented to general practice in Australia representing 4.2 of every 100 encounters.(1) Typically a self-limiting illness, URTI symptoms usually peak between days 2-4, decreasing in severity until resolution of illness in 7-10 days.(2) Therapeutic guidelines recommend against antibiotic treatment for viral URTI, and suggest that antibiotics would be indicated in only a small proportion of cases of pharyngitis, acute rhinosinusitis and acute otitis media.(3, 4) Recent research recommends reducing prescription rates in general practice to combat development of antibiotic resistance as primary care accounts for a large proportion of antibiotic use worldwide.(5-8) However the rate of prescribing for acute respiratory infections in Australia continues to exceed recommendations.(5)

Delayed prescribing is one of the strategies suggested to reduce prescription rates for URTI.(6, 9) Despite the fact that it has been shown to be safe, does not alter clinical outcomes, and is effective in prescription reduction, (10-16) there are still barriers to the uptake of this strategy. Clinicians raise concerns about diagnostic uncertainty; first presentations of URTI are not predictive of severity or duration(17) and without near-patient tests the aetiology cannot be objectively determined. Clinical acumen is therefore a vital component of this strategy. Some GPs are also uncomfortable with leaving decision-making to patients or suggest that it sends mixed messages about antibiotic effectiveness.(18) Others view delayed prescribing as an unnecessary compromise to meet

patient expectation or allay patient fears when no prescription is the preferred alternative.(19) The lack of consistent guidelines for implementation of delayed prescribing also limits uptake.(9, 19)

Effective management of the consultation is a key consideration. Clinicians commonly report conflict when immediate prescription of antibiotics is not offered and some physicians report that delayed prescribing strategies help with managing these situations.(20) Patients, in general, strongly believe in the effectiveness of antibiotics(14) although patient expectation of antibiotic prescription seems to be reducing from previously reported high levels.(21, 22) A recent study reports patients visit their GP primarily due to the severity or persistence of symptoms, or the need for reassurance that treatment is not required.(22) In this study patients tended to expect antibiotics if they felt symptoms were severe although a quarter of those prescribed antibiotics did not complete the course.(22)

For many patients a request for antibiotics is most likely a request for symptom relief. While there is evidence that delaying antibiotic prescription causes no harm, there is limited evidence for how to advise patients in the interim. An understanding of patients' experience of URTI once they have left the GPs office will provide further evidence to assist management strategies and support uptake of delayed prescribing. This project aims to monitor patients' experience of URTI in real-time after prescription of antibiotics for URTI in general practice.

Methods

Practice recruitment

General practices across Australia already using the SmartVax tool, smartphone monitoring of symptoms following immunisation, (23) were invited to take part in the study. 22 practices comprising 32 individual clinic sites across Australia agreed to participate. None of the practices used near patient tests to diagnose URTIs.

Data extraction tool and patient recruitment

Patients were automatically identified by data extraction software embedded in the resident SmartVax program within each clinic. The software sent an SMS invitation to anyone over the age of 12 who was prescribed a course of a named antibiotic as indicated in therapeutic guidelines as commonly prescribed for URTI.(3) This included penicillins (amoxicillin, phenoxymethylpenicillin, amoxicillin/clavulanic acid, flucloxacillin) macrolides (azithromycin, roxithromycin, clarithromycin, erythromycin) and cephalosporins (cephalor monohydrate, cephalexin, cefuroxime axetil). Information posters were placed in each clinic to advise patients they may receive an SMS invitation for the study. This approach captured a larger cohort of patients, some of whom did not present with URTI but were selected for the study because an antibiotic had been prescribed. At the time of conducting this study it was not technically feasible to automatically select for recruitment in any other way. Patients receiving antibiotic prescriptions for URTI were later identified from this larger cohort using the protocol described (Supplementary Table 1, Supplementary Figure 1).

Real-time monitoring of patients

Adults and children over 12 years of age were included. Parents or guardians were invited to respond to the survey on behalf of their children. An SMS invitation was sent from the

practice software in each clinic to all identified patients within 72 hours of receiving an antibiotic prescription. Patients wishing to participate activated the SMS link to a Uniform Resource Locator (URL) and completed the informed consent document and online survey instrument. The online survey was optimised for the mobile platform so respondents could complete all documents on their phones. Only responders to the first survey received a second SMS text seeking the same information on day 7 post GP visit. All SMS invitations and survey completions were timestamped so that the day of response could be determined.

Survey Instrument

The survey comprised two parts: general questions on antibiotic use, commencement and completion, and symptom management as well as the Wisconsin Upper Respiratory Symptom Survey (WURSS-24). The WURSS-24 is a short-form of a validated questionnaire that was developed to evaluate the impact of URTI over time.(24, 25) It comprises 24-items in two domains that assess symptom severity and quality of life.(25) Participants rate the presence and severity of each item on a 7-point Likert-type scale. The symptom severity scores range from “not present/no impact” (0); “very mild” (1); “mild” (3); “moderate” (5) to “severe” (7). A global severity score is obtained by summing items 2 to 23. Embedded within the WURSS-24 is the WURSS-21 which is identical except for the omission of 3 items from the symptom domain: headache, body ache and fever which further discriminate influenza-like illness. The WURSS-21 yields similar global severity scores to the WURSS-24. Permission and registration to use the WURSS-24 was obtained from the Wisconsin Alumni Research Foundation (WARF).

Identification of URTI-specific population

We defined URTI as any acute infection of the upper respiratory tract (Supplementary Table 1) with symptoms of headache, sneezing, chilliness, sore throat, nasal discharge, nasal obstruction, cough, or malaise. At least two symptoms needed to be present to be defined as URTI, and at least one of those two symptoms must be either early symptoms of nasal discharge/obstruction or sore throat or a later symptom of cough. URTI-specific presentations were discriminated from other RTIs and presentations of non-related conditions by applying the protocol outlined in (Supplementary Table 1, Supplementary Figure 1).

Sample Size

The sample size calculation was based on an estimate of the WURSS-21 by Barrett and colleagues who found that the minimal important difference (MID) which represented the mean day-to-day change for participants showing minimal improvement was 9.48 points per day of the sum total score.(24) The corresponding Guyatt responsiveness index, a direct correlate of a clinically significant effect size, was 0.8. The authors suggest a sample size of 74 would have 90% power to detect a clinically significant difference in global severity scores over time assuming $\alpha=0.05$; $\beta=0.1$ and two-tailed testing.(24) Using Barrett's evaluation of sample size we applied the following assumptions: at least 70% of the antibiotic prescriptions identified by the data extraction tool would be URTI specific; a response rate of 50%; and an attrition rate of 30% between responders to the first SMS and those responding to both the first and second SMS. Based on these assumptions, a sample size of 302 would be required to be able to robustly track symptom profile over time.

Data Analysis

Survey responses were sorted by timestamp and allocated to the day of response post GP visit. If the survey response was logged more than 72 hours after the patient received the SMS invitation, the survey was excluded as invalid. Median scores (as opposed to mean scores to mitigate against extreme variations in the sample) were calculated for each item of the WURSS-24. Global symptom severity scores were calculated by summing items 2-23. Descriptive statistics were used to quantify the demographic profile of the URTI-specific population and survey responses.

Results

Survey responders

A total of 8218 SMS invitations were sent over the peak RTI season from June to October, 2017. This period corresponded with the worst influenza season on record in Australia since the 2009 pandemic(26) resulting in large numbers of presentations of all types of RTI in general practice. The overall response rate to real-time monitoring of patients in general practice is shown in Supplementary Table 2.

Identification and characteristics of the URTI-specific population

The URTI-specific population was identified from a larger cohort of patients receiving antibiotics that are commonly prescribed for URTI using the protocol described (Supplementary Table 1, Figure 1). The included and excluded participants are shown in Figure 1. Of the 8218 SMS sent, 4089 of these presentations could be identified as URTI-specific and were included in the study. Excluded invitees were both responders and non-responders. Responders to the survey were excluded if the survey data did not indicate URTI symptoms were present and instead indicated either a different RTI (N=68) or prescription

for an unrelated condition (N=88). 29 surveys were excluded as invalid due to a delayed response to the SMS. Non-responders were excluded from the URTI-specific population if: the prescription was recorded as non-URTI such as lower respiratory tract infection (LRTI) or pneumonia (N=1293); the prescription was for an unrelated condition (N=1702); or if the prescription or visit reason was not stated (N=949). The URTI-specific population is considered to be an underestimate due to the large amount of missing data (N=949) that was not coded on their computers by the participating GPs.

Of the 4089 presentations that could be identified as URTI-specific, 614 patients responded to the first SMS and 246 of these responded to day 7 survey as well. 3475 patients who presented for URTI did not respond to any survey. The response rate for the URTI-specific population was 15%. The demographics of the URTI-specific population is shown in Table 1. There was no clear gender difference comparing responders to non-responders. However, there was a trend that male responders tended to be slightly older than male non-responders.

The distribution of antibiotic type within the URTI-specific population is variable across the antibiotic classes of penicillins, macrolides and cephalosporins (Supplementary Table 3). The majority of responders (541 of 614; 88.1%) reported that they commenced antibiotics on the day they visited their GP; 30 (4.9%) two or three days after visiting their GP; 11 (1.8%) reported commencing and then ceasing antibiotic treatment; and 43 (7%) did not commence.

Symptom severity of patients receiving antibiotics for URTI conditions

The number of survey responses logged for each day post prescription are shown in Table 2 together with the median global severity score and interquartile range. Global severity scores were highest on day 3 and declined steadily to day 10.

The subset of patients (N=246) that completed surveys at both 72 hours and 7 days post GP visit had a median global symptom severity score of 41.5 (IQR 24, 62) at 72 hours declining to 10 (IQR 3, 21) at day 7. Only 13 of these 246 patients (5.3%) did not show a reduction in global severity score from 72 hours to day 7 indicating the majority of this subset are following a typical time-course of self-limiting acute URTI.(24, 25) The MID of the WURSS21 is 9.48.(24) The WURSS-24 would be expected to be only marginally higher given that it is identical except for the addition of 3 items. Based on this inference only 4 of the 13 patients with no reduction in day 7 scores showed a greater than 9.5 point difference in their severity score at 72 hours. Therefore 4 of 246 patients (1.6%) showed worsening symptoms, 9 (3.7%) had the same severity score at 72 hours and day 7; and 233 (95%) showed symptom improvement. It should be noted that is not possible to quantify how long each patient in our cohort was ill for before attending the GP and this may have varied between participants.

Incidence and frequency of symptoms

There was considerable variation in the presence of symptoms between participants and over time. This is not unexpected as the cohort had a wide range of clinical conditions (Supplementary Table 1) and is characteristic of URTI. The frequency and median symptom severity for each item of the WURSS-24 assessed on 3 and 7 days post prescription is shown in Table 3. Item 1 of the WURSS-24 is an overall global assessment of how sick patients feel

on the day they complete the survey. By 3 days post GP visit the median score is 3 (IQR 2,5) indicating patients experienced mild to moderate symptoms. By day 7 post prescription patients report a median score of 1 (IQR 1,3) indicating only very mild to mild symptoms at this time-point.

At least 50% of the URTI-specific population experience symptoms of runny nose, tiredness, cough and headache 3 days post GP visit and rate these symptoms as a score of 1 (very mild) or higher (Table 3). Cough and tiredness have the highest median symptom severity (4; "mild to moderate") of any of the assessed symptoms at day 3 and correlated with the QOL impact where patients report an inability to sleep well (item 16). Symptoms of nasal congestion correlate with the reported QOL impact of breathing easily (item 17). By day 7 post GP visit the only symptom experienced as very mild or higher is cough which still effects more than 50% of the cohort.

Patient experience of URTI "How sick do I feel?"

Further evaluation of item 1 of the WURSS-24 "How sick do I feel?" for each day post GP visit is shown in Figure 2. We have proposed a time-course of infection. This is a projection based on the premise that the majority of patients do not consult a GP the first day (within hours) that symptoms present. The earliest patients would be expected to present to the GP is day 1 of their infection. Data captured three days post visit to the GP are therefore projected to correlate at the earliest with day 4 of the projected time-course of infection. It is not possible to accurately predict when patients first became ill prior to their GP visit. Overlayed on this projection is the documented time-course for a community-acquired URTI population assessed using the WURSS. The pattern of symptom severity is similar over time indicating a common trajectory. The URTI-population described in the literature received no

antibiotic or symptomatic treatment suggesting that the prescription of antibiotics for the cohort in this study did not hasten their recovery.

Discussion

Summary

We were able to monitor patients presenting to general practice with URTI who were prescribed antibiotics using data extraction software and SMS technology. These patient were prescribed antibiotics based on their symptom profile at the time of presentation. Overall patients report experiencing only mild to moderate symptoms by 72 hours post GP visit, reducing to very mild or not sick according to the fewer numbers who responded by day 7. Most patients reported that they completed their antibiotic treatment. Although this was not independently verified and may not be reliable.

Comparison with other studies

Observation of this clinically diagnosed URTI population showed that the pattern of global symptom severity scores over time is consistent with community-acquired viral URTI severity scores assessed using the same instrument as reported in the literature.(24, 25) This is a common pattern of overall symptom severity and duration consistent with viral URTI.(2, 24, 27, 28)

Patients experienced different symptoms and these varied over time as would be expected with URTI.(2, 27) The severity of each symptom, when present, was also variable but very few patients experienced severe symptoms by 3 days post GP visit. The most problematic symptoms for patients after visiting their GP were headache, runny nose, tiredness and cough; the latter being the most frequent, severe and prolonged symptom consistent with what is known about viral URTI.(29) The projected pattern of symptom severity over time

for the observed population is consistent with URTI-specific populations reported in the literature using the same outcome measure(25) and who have not received any treatment or symptom modifying medication. This suggests that the observed population receiving antibiotic treatment did not experience reduced symptom severity or a more rapid resolution of symptoms. Other studies support these findings showing antibiotic treatment does not impact URTI symptoms(14, 16) with the exception of a modest reduction in complications for sore throat.(15)

Strengths and weaknesses of the study

Despite a modest response rate to the survey, this prospective study sampled a large number of patients in an Australian general practice setting. It reports the experience of patients who have received antibiotic prescription for URTI and their evaluation of symptom severity. This type of real-time monitoring of patient outcomes does not rely on participant recruitment by GPs nor does it impact on the consultation as recruitment occurs after the patient has left the doctor's office.

Self-selection and social desirability bias may account for the higher than expected proportion of respondents claiming to commence and continue antibiotic treatment compared to previous studies in a primary care setting.(30) It is possible that potential participants who did not commence nor complete the antibiotic treatment did not respond to the survey at either or both time points. The modest response rates suggest that generalisability of these results should be interpreted cautiously.

Additionally there inaccuracies and missing data in practitioner coding such that it was not possible to reliably identify URTI-specific presentations by visit or prescription reason. Instead identification of the URTI-specific population used a systematic protocol as

described. For technical reasons SMS invitations were not issued over the weekends of the data collection period so patients due to receive their 72 hour or day 7 SMS invitations did not receive them until the next business day. This limitation was addressed by timestamping all SMS invitations and survey responses so the day of response post GP visit could be determined.

Clinical implications and conclusions

The results of this study appear to add more evidence in support of delayed prescribing. The majority of participants experienced mild to moderate symptoms 3 days post GP visit and report marked improvement after this time point. By comparison with the literature, antibiotic treatment was shown to have no effect on symptom severity or duration.

Symptom management for 48 hours post GP visit may support a delayed prescribing strategy for those patients who are not severely ill or septic at the time of presentation. Doctors can foster a patient-centred approach to URTI management by acknowledging the severity of symptoms and offering patients a structured symptom management plan. Within the limitations outlined above, this study provides some evidence to guide patients on the symptoms trajectory such that significant variations from this pattern might prompt re-consultation for review. We posit that this approach will improve both satisfaction and enablement.

Declarations

Ethics approval

Ethics approval for this project was received from the National Research and Evaluation Ethics Committee of the RACGP (NREEC 16-008) and the University of Notre Dame Ethics

Committee (approval number 017034S). Participants provided informed consent prior to participation in this study.

Funding

Financial support for this project was received from the Royal Australian College of General Practitioners (RACGP) via a competitive grants process. Funds were supplied via the HCF Research Foundation/RACGP Research Grant Scheme (project HCF 16b 561505).

Competing interests

All authors have no conflicts of interest to declare.

Acknowledgments

We wish to thank Karin Orlemann for her assistance with practice recruitment and follow-up. We also wish to acknowledge all of the GPs, practice staff and patients of the participating GP clinics who generously gave of their time to assist with this study.

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Figure Legends

Figure 1. Application of the protocol to identify the URTI-specific population of patients presenting to Australian general practice in 2017.

Figure 2. Perception of illness severity after prescription of antibiotics of patients presenting to Australian general practice in 2017. Responses to Item 1 of the WURSS-24 "How sick do you feel today?" for each day are represented. The item is rated on an 7-point scale from not sick (0) to severely sick (7). The boxes represent the median (notch), first quartile (dark grey) and third quartile (light grey). Ends of the vertical lines represent the maximum and minimum values. The data collected at 3 days post GP visit are proposed to correlate with day 4 of the infection time course. The dotted line compares, from the literature, the median symptom score for item 1 of the WURSS-21 (which is the same as the WURSS-24) from a population with community acquired viral URTI who received no treatment and whose time course of infection is known.[22] Note that the sample size for each day varies as shown in Table 2.

Table 1. Demographic profile of the identified URTI-specific population of patients presenting to Australian general practice in 2017.

		URTI- specific responders	URTI-specific non-responders	Overall
Total N		614	3475	4089
Response rate		15%	85%	
Median age	male	43 (IQR 32,60)	37 (IQR 24,50)	
	female	40 (IQR 31,55)	38 (IQR 27,52)	
	range	12-89	13-95	
	overall	41 (IQR 31,56)	38 (IQR 26,51)	
Age male	12-14	8 (1.3%)	54 (1.6%)	
	15-24	13 (2.1%)	256 (7.4%)	
	25-44	51 (8.3%)	477 (13.7%)	
	45-64	45 (7.3%)	282 (8.1%)	
	65-74	17 (2.8%)	89 (2.6%)	
	75+	5 (0.8%)	39 (1.1%)	
	total	139 (22.6%)	1197 (34.5%)	1336 (32.7%)
Age female	12-14	14 (2.2%)	70 (2.0%)	
	15-24	47 (7.5%)	393 (11.3%)	
	25-44	215 (35.0%)	974 (28.1%)	
	45-64	157 (25.6%)	610 (17.6%)	
	65-74	30 (4.9%)	163 (4.7%)	
	75+	10 (1.6%)	63 (1.8%)	
	total	473 (77.0%)	2273 (65.5%)	2746 (67.2%)
	Sex not recorded	2	5	7 (0.2%)

Table 2. Median global symptom severity scores for each day post prescription for patients presenting to Australian general practice in 2017. Asterisk denotes a sample size less than 20.

Day post prescription	Survey Responses (N)	Median WURSS24 Global severity score
3	353	39 (IQR 20,63)
4	137	41 (IQR 26,58)
5	106	33 (IQR 17,56)
6*	12	24 (IQR 10,42)
7	181	11 (IQR 4,28)
8	31	12 (IQR 5,19)
9	30	4 (IQR 1,12)
10*	10	14 (IQR 8,15)

Table 3. Symptom severity and frequency of WURSS-24 items at 3 and 7 days post antibiotic prescription for patients presenting to Australian general practice in 2017. Symptom severity is the median severity of each item on a 7-point scale. Frequency represents the percentage of participants experiencing the symptom at that timepoint. The symptom was considered present at the timepoint if the participant recorded a symptom severity score of 1 or higher for the WURSS-24 item. Sample size for patients completing surveys at each timepoint were N=353 (Day 3) and N=181 (Day 7).

WURSS-24 Item	Descriptor	Median Symptom Severity Score Day 3	Frequency (%) symptom score ≥1 Day 3	Median Symptom Severity Score Day 7	Frequency (%) symptom score ≥1 Day 7
1	How sick do you feel today?	3 (IQR 2,5)	97.2	1 (IQR 1,3)	79.0
Please rate the average severity of your cold symptoms over the last 24 hours for each symptom:					
2	Runny nose	1 (IQR 0,3)	50.4	0 (IQR 0,2)	43.6
3	Plugged nose	0 (IQR 0, 4)	43.9	0 (IQR 0,1)	25.4
4	Sneezing	0 (IQR 0,1)	28.3	0 (IQR 0,0)	14.9
5	Sore throat	0 (IQR 0,4)	43.1	0 (IQR 0,0)	14.4
6	Scratchy throat	0 (IQR 0,3)	35.1	0 (IQR 0,0)	14.9
7	Cough	4 (IQR 2,5)	80.5	1 (IQR 0,4)	58.6
8	Hoarseness	0 (IQR 0,4)	37.7	0 (IQR 0,0)	18.8
9	Head congestion	0 (IQR 0,4)	48.2	0 (IQR 0,1)	26.0
10	Chest congestion	0 (IQR 0,3)	32.9	0 (IQR 0,0)	18.8
11	Feeling tired	4 (IQR 0,5)	69.7	0 (IQR 0,4)	47
12	Headache	2 (IQR 0,5)	56.9	0 (IQR 0,2)	29.8
13	Body ache	0 (IQR 0,3)	32.9	0 (IQR 0,0)	13.8
14	Fever	0 (IQR 0,0)	22.1	0 (IQR 0,0)	4.4
Over the last 24 hours, how much has your cold interfered with your ability to:					
15	Think clearly	0 (IQR 0,4)	45.3	0 (IQR 0,1)	25.4
16	Sleep well	4 (IQR 0,5)	65.7	0 (IQR 0,3)	34.8
17	Breathe easily	3 (IQR 0,5)	58.6	0 (IQR 0,2)	30.4
18	Walk/Climb stairs	0 (IQR 0,5)	41.4	0 (IQR 0,0)	22.7
19	Accomplish daily activities	0 (IQR 0,5)	47.9	0 (IQR 0,0)	15.5
20	Work outside the home	0 (IQR 0,5)	41.9	0 (IQR 0,0)	16.0
21	Work inside the home	0 (IQR 0,4)	28.3	0 (IQR 0,0)	11.0
22	Interact with others	0 (IQR 0,4)	35.1	0 (IQR 0,0)	13.3
23	Live your personal life	0 (IQR 0,5)	40.8	0 (IQR 0,0)	17.7