Central diabetes insipidus from a patient's perspective

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Central diabetes insipidus from a patients' perspective: management, psychological co-morbidities, and re-naming of the condition - results from an international web-based survey

--Manuscript Draft--

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Abstract:	BACKGROUND Central diabetes insipidus (cDI) is a rare neuroendocrine condition. Data on treatment-related side-effects, psychological co-morbidities, and incorrect management are scarce. The aim of this survey was to investigate patients' perspectives on management and complications of cDI, psychological co-morbidities, patients' perspectives on the degree of knowledge and awareness of the condition amongst healthcare professionals, and views for re-naming cDI to avoid confusion with 'diabetes mellitus'(DM). METHODS A cross-sectional web-based anonymous survey, developed by endocrinologists and patient representatives, assessing management of cDI, psychological co-morbidities, and level of awareness amongst healthcare professionals. FINDINGS In total, 1034 patients with cDI participated, 47%(n=488) with isolated posterior and 53%(n=546) with combined anterior/posterior pituitary dysfunction. Main

	aetiologies were idiopathic 30%(n=315) and tumours/cysts (pre-surgical 21%(n=217), post-surgical 25%(n=254)). Among patients on desmopressin therapy, 26%(95%-CI [0·24-0·29];n=273/994) experienced hyponatraemia leading to hospitalisation. Patients who routinely omitted/delayed desmopressin to allow intermittent aquaresis had a significantly lower prevalence of hyponatraemia compared to those not aware of this approach (OR 0·55; 95%-CI [0·39-0·77]; p=0·0006). During hospitalisation, around one in seven patients (95%-CI [0·10-0·16]; n=71/535) did not receive desmopressin while in a 'nil by mouth'/'nil per os' state without intravenous fluid replacement and reported symptoms of dehydration. In total, 64%(95%-CI [0·61-0·67];n=660) reported lower quality of life and 36%(95%-CI [0·33-0·39];n=369) recognised psychological changes subjectively related to their cDI. Eighty percent (95%-CI [0·77-0·82];n=823) encountered a situation where cDI was confused with DM by healthcare professionals, and 85%(95%-CI [0·83-0·88];n=884) supported re-naming of the condition; the most favoured being 'vasopressin deficiency' or 'AVP deficiency'. INTERPRETATION This is the largest survey of patients with cDI, reporting a high prevalence of treatment-related side-effects, mismanagement during hospitalisation, psychological co-morbidities, and a clear support for re-naming the condition. Our data are the first to indicate the value of routinely omitting/delaying desmopressin. FUNDING Swiss National Science Foundation; Swiss-Academy of Medical Sciences and G.&J.Bangerter-Rhyner-Foundation.

Manuscript reference number: THELANCETDE-D-22-00438
Title: Central diabetes insipidus from a patients' perspective:
management, psychological co-morbidities, and re-naming of the condition

Dear Dr Holmes,

We are pleased to submit our revised manuscript with the title "Central diabetes insipidus from a patients' perspective: management, psychological co-morbidities, and re-naming of the condition".
We wish to thank the editors and reviewers for the careful and detailed comments, which allowed for us to considerably improve our manuscript.

Please find below in detail our responses to all the reviewers' comments. Changes are highlighted in the revised manuscript accordingly.

General points to the Editor:

1.) According to reviewers' requests and formatting guidelines (word limit), we have moved some sections to the supplementary material. In addition, the *breast-feeding* section and the corresponding discussion has now been removed from the revised article. However, if the editor wishes, we are happy to include this to the supplementary. Our current word count is now 4040.

2.) For methodological and statistical aspects, we have been actively supported by Dr Lars Hemkens in the revision process. He is an epidemiologist and Deputy Director, Basel Institute for Clinical Epidemiology & Biostatistics, with expertise in *Routinely collected health data*, *Pragmatic trials and novel study designs*, and *Meta-Research*. We would therefore like to have him as co-author and have obtained the consent of all other co-authors. The required signed document will be prepared and submitted as soon as possible.

Sincerely,
Mirjam Christ-Crain

EDITORS' SPECIFIC POINTS:

1. Please have each author complete an ICMJE form and upload these as Companion files when you submit your revised article.

All authors have completed the ICMJE form, and all files are uploaded accordingly.

2. Please have each author sign a completed Author Statement form and upload these when you submit your revised article.

All authors have signed the Author Statement form, and all files are uploaded accordingly.

3. On the title page, please add 'Prof' before any author names who are full professors.

We added 'Prof' before all full professors.

4. In the Summary, please add the aim of the study to the Background section.

We added the aim of the study to the abstract.

5. In Tables 1, can data be added on race/ethnicity and/or geographical location.

Unfortunately, due to anonymity of our survey, we were not allowed to collect data on race/ethnicity and/or geographical location.

6. The Contributor statement in the article needs to state who verified the data and who had access to raw data and who had final responsibility for the decision to submit for publication.

All authors had access to all the data and had final responsibility for the decision to submit for publication. This information was now moved from the Methods section to the Contributor statement.

7. For the four people named in the Acknowledgments section, we require email confirmation stating that they are happy to be named in the article. Please collate these email confirmations and upload as a Companion file when you submit your revised article.

We have uploaded the e-mail conformation of all four accordingly.

8. Please provide the appendix as a single document, in pdf form, with page numbers, and a Contents page. When referring to supplementary material in the article, please use the format appendix pX rather than for example figure 4S.

The appendix has been revised and uploaded according to the formatting guidelines. References in the manuscript has been changed accordingly.

9. Items in the appendix should be numbered from 1; ie, figure 1S, rather than continuing the numbering system from the article.

We have changed the numbering of figures / tables in the appendix accordingly.

10. Please include the actual survey in the appendix and confirm whether the survey was validated.

We attach the questionnaire with the current re-submission (please see appendix CRF). The survey was developed and approved by patients' representatives from the United States and used for the first time for this study. Also, the relevant Ethics Committee had approved this questionnaire as appropriate for this study.

11. please upload the article tables as a single Tables file (word doc) rather than each table separately.

We have uploaded a single tables file as a word document.

EDITORS' GENERAL POINTS:

- Our revised paper has 4040 words and 29 references
- Subheadings in the Results are removed in the revised manuscript.
- We included a study descriptor to the title— "results from an international web-based survey"
- References are now in Vancouver style.
- We have 5 non-text items (3 figures and 2 tables) in the revised article

REVIEWERS' COMMENTS:
Note that reviewer numbers are allocated by the system at invitation and not at completion of reviews, so some numbers might be missing.

Reviewer #1:

We learn from patients with rare diseases and this survey of 1034 patients with central diabetes insipidus (cDI) is an eloquent demonstration. cDI patients are inadequately recognized in 80% of cases and confused with patients with diabetes mellitus. Hence, 83% of cDI patients would like to rename the condition "AVP deficiency". In the same vein, patients with nephrogenic diabetes insipidus (Bockenhauer, D., Bichet, D.G. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. Nat Rev Nephrol, 11: 576-88, 2015.) when admitted to the hospital or when seeking health insurance, are also confused with patients with diabetes mellitus and this condition should be renamed "AVP resistance". I would favor AVP deficiency/AVP resistance since the three letters AVP are a reminder of the dDAVP treatment effective in AVP deficiency and tested non-effective in AVP resistance.

*We thank the reviewer for this important reference which we included in the revised manuscript. We agree and share the experience that confusion occurs for both forms of diabetes insipidus, central and nephrogenic. In fact, based on an ongoing international working group discussion considering possible alternative names for central and nephrogenic DI, the suggested names are **AVP deficiency and AVP resistance.***

The data obtained from this large survey augment the observations published previously from individual diabetes centers. We are used, after Maghnie et al. (ref 9) to look for anterior pituitary dysfunction and Figs 1 and 2 are providing relative frequencies for post-surgical (25%) and pre-surgical hypothalamic/Pit. tumor cysts. I am concerned with the high percentage (26%) of patients with hyponatremia leading to hospitalization. I encourage my cDI patients to practice "dDAVP drug holidays" that is to stop or delay one dose of dDAVP during a weekend, at regular intervals, i.e., every 6 months, and observe at what time they return to a polyuro-polydipsic state. They could then deduce the minimal amount of dDAVP necessary to control their AVP deficiency and prevent episodes of hyponatremia. This precautionary measure is important for aging patients with DI since, for unknown physiological reasons, that is not related to a normal decrease in glomerular filtration rate with age, there is less polyuria in aged patients in both AVP deficiency and AVP resistance. AVP-deficient patients will need less dDAVP after 65, a rare benefit of aging! Some unanswered questions are also part of this survey. We are not used to measure oxytocin during hypertonic saline or arginine testing (Fenske W et al. N Engl J Med. 2018 Aug 2;379(5):428-439; Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study; Lancet 2019; 394: 587-95). Yet, Catherine Dulac' group demonstrated that the typical preference of male mice for females was eliminated in mutants lacking oxytocin, a neuropeptide modulating social behaviors in many species and that ablation of the oxytocin receptor in aromatase expressing neurons of the medial amygdala fully recapitulates the elimination of female preference in males (Yao et al. eLife 2017;6: e31373.). Whether a potential deficit in oxytocin could explain the sexual arousal data of Fig 5S will need to be documented by many measurements of oxytocin plasma levels in AVP deficient patients.

We appreciate this point brought up by the reviewer and agree that there is increasing evidence that patients with diabetes insipidus might be at high risk for an additional oxytocin deficiency and this may (at least partly) explain sexual dysfunction and lower quality of life/psychological burden. However, most data are from animal studies with limited data from human studies. Studies on a possible oxytocin deficiency in humans are urgently needed. This issue is discussed on page 18/19 of the revised manuscript.
*A recently published review nicely summarizes this hypothesis (**Ref**. Clarke L, Zyga O, Pineo-Cavanaugh PL, et al. Socio-behavioral dysfunction in disorders of hypothalamic-pituitary involvement: The potential role of disease-induced oxytocin and vasopressin signaling deficits. Neurosci Biobehav Rev. 2022:104770.)*

Minor comments/questions:

More female cDI patients admitted for hyponatremia?
We now performed an additional analysis to investigate sex differences in hyponatremia:

In total, 27% (95%-CI [24, 30]; n=213/794) females experienced hyponatraemia leading to hospitalisation in comparison to 25% (95% CI [20, 30]; n=60/240) in males, with no difference between these groups (estimated difference: 2%; 95% CI [-8, 5]; p=0·6320).

More elderly female patients admitted for hyponatremia?
Unfortunately, we did not collect data on the age at the time of hyponatraemia but instead looked at the cumulative events, and, therefore, cannot not answer this question; however, we performed an additional analysis to compare the hyponatraemia rate in male and female patients over the age of 60:

In patients over the age of 60, 37% (95%-CI [0·28-0·46]; n=42/113) females experienced hyponatraemia in comparison to 41% (95%-CI [0·22-0·59]; n=11/27) in males, with no difference between these groups (estimated difference: 4%; 95% CI [-0.19, 0.26]; p=0·9021).

Were hyponatremic patients likely to take other drugs like hydrochlorothiazide or drugs inhibiting the recapture of serotonin?
Thank you for this query. We aimed to design the questionnaire with as many questions as needed to answer our most urgent points. At the same time, we were keen to avoid overloading patients with too many further questions in order to achieve as high a rate of complete responses as possible. Therefore, unfortunately we did not collect data on medications, such as HCT or SSRI.

Any hyponatremic cDI patient with a clear evidence of transient volume contraction secondary to volume loss, usually gastro-intestinal, should we teach our cDI patients to decrease their dDAVP, replete volume and check their plasma sodium if they suspect a total body sodium deficit?
Again, we did not ask the patients specifically on the context in which situation the hyponatremia developed. However, we agree with the reviewer that standard recommendations for patients with DI on how to react in situations with expected volume loss (typically gastro-intestinal losses), would clearly be needed, i.e., decrease of desmopressin dose, drink to thirst, replete volume and check plasma sodium levels.

Reviewer #2:

This is a well executed web based voluntary study based on the information given by patient's with the diagnosis of diabetes insipidus. This unusual methodology does provide a satisfactory amount of useful and sometimes novel information.
There is excellent coverage in the paper by its discussion of the conflict and misunderstanding that exists between diabetes mellitus and diabetes insipidus.

An important problem for patients with diabetes insipidus is a possibility of developing hyponatremia as a result of treatment with desmopressin and mismanagement of fluid intake. A warning is given, however, it is not clearly delineated as a result of improper management of desmopressin and fluid intake. The paper would be enhanced if this were clarified, particularly with the use of citing carefully developed regimens for pediatric patients which have not considered separately within the study group.
Thank you for raising this important point. We now more clearly emphasise the fact that hyponatraemia is a problem especially for those patients in whom desmopressin intake and fluid intake are not managed appropriately. We now cite the literature quoting the need for careful regimens in paediatric patients. See lines 549-551, page 17.
*(e.g., **Ref:** Challenges and improvement needs in the care of patients with central diabetes insipidus. H Teare, J Argente, M Dattani, J Leger, M Maghnie, M Sherlock, G-C Ali, J Francombe, S Marjanovic.)*

The discussion of the advantage of desmopressin given by oral methods rather than nasal or infra venous is well described and should be emphasized.
Thank you, we agree that oral preparations of desmopressin treatment should be preferred. This is now further emphasised in the manuscript. See line 529, page 17.

The authors emphatically state that we should consider a clear differential nomenclature that separates diabetes mellitus from diabetes insipidus, and they recommend an abbreviation for diabetes insipidus to be cDI. Indeed, this or something close to it should be considered to avoid confusion and treatment errors.
*Thank you for this positive comment. In fact, based on an ongoing international working group discussion considering possible alternative names for central and nephrogenic DI, the suggested names are **AVP deficiency** and **AVP resistance** which would avoid the confusion with "diabetes mellitus". See line 652, page 19.*

Reviewer #3 (Statistical Reviewer):

Overall Comments

The study represents potentially interesting results, but it does need more detail around the methods which I have highlighted

Major Comments

1. Can you please complete an appropriate reporting checklist. The study falls under several but can I ask for you to complete STROBE checklist which seems the most appropriated.

We completed the STROBE checklist as suggested, see attached.

a. When quoting all point estimates including prevalence estimates can you please also quote 95% CI

We agree, for prevalence estimates 95%-CI should be quoted.

We included 95%-CI for prevalence estimates of dysnatraemia, hyponatraemia, hypernatraemia, given 'desmopressin escape' category proportions, desmopressin access problems, incorrect management during hospitalisation, psychological co-morbidities, confusion rate with 'diabetes mellitus', and proportion patients in agreement with re-naming. This is also mentioned in the methods section now.

b. Throughout when making comparisons can you please quote point estimates and 95% for the estimate of effect. Generally if there is a P-value must have a CI.

Thank you for pointing on this. We now have removed the 'breastfeeding section' with comparisons in response to the feedback of reviewers (and word limitation) from the manuscript.

c. Generally a limitation is looking at data from a single centre.

i. Did this centre have national coverage?

The data collection was via the server of the University Hospital Basel, Switzerland; however, the survey was accessible globally and patients were invited globally to participate. This method was chosen to include a wide spectrum of patients aiming to maximize generalizability of the data.

ii. What level of regional coverage it have.

As stated in 1.c.ii., patients were invited globally regardless of whether they are seen in a pituitary center or a non-expert center or by a general physician. In order to protect anonymity, we were not allowed to collect data on the country/region of residence. We have added this to the limitations section. See page 20.

d. The paper needs to have text in discussion commenting on the limitations of the study

i. There is no mention of bias within the context of your own study. By definition an analysis such as this will be biased. It is just a case of minimising it

We agree with the reviewer and now include a limitations section in the discussion and highlight that we can only aim for minimizing selection biases and maximizing the spectrum of patients, fully acknowledging that our sample is not a random sample. This includes, among others, a specific discussion of selection bias and re-call bias (see our answer below). There may be a bias due to a more engaged population of patients responding. If this is the case, it likely represents the best-case scenario, and it may be that the general situation is in fact worse than reflected in this survey. A possible but less likely scenario is that patients who only have had negative outcomes responded, in which case the general situation may in fact be better. See page 20.

ii. There is also no discussion of confounding in the context of the study

Thank you for raising this important point – we now highlight that our study design (as survey) cannot provide evidence on causal relationships due to confounding. We now discussed this important point and included this in the limitation section. See page 20.

iii. From experience I would expect the coverage and quality of the data sets to vary by factors such as age, sex and/or education.

We agree that this is an important issue. In the study planning and conception of the questions for the survey; however, much attention was paid to ensuring that the questions were as clear as possible in easy-to-understand language with clear answer options (e.g., all medical terms were explained or replaced by alternative words).

The involvement of patient representatives who supported us in this step was particularly helpful. We have chosen this approach in order to minimise the variability of quality due to factors such as age, gender, and education.

iv. Have discussed issues with self-reported data but there will also be issues with recall bias

We agree that recall bias is an issue and now discuss this point in the limitation section. Reassuringly, outcomes such as hospitalisation with dysnatraemia, confusion with diabetes insipidus, incorrect management during hospitalisation are often significant events that patients remember very well. We, therefore, believe that recall bias in the outcomes collected is only a minor problem. We have, however, discussed it in the limitation section. See page 20.

v. The paper is only looking at a snap shot in time and not at longitudinal effects

We absolutely agree and we do not aim to establish causality with this research design. We now have explicitly stated this as limitation, specifically note that this is an explanatory and descriptive.

We carefully checked that we make no causal claims. Many of the findings, e.g., psychological co-morbidities in patients with isolated diabetes insipidus and the role of the desmopressin escape method, need to be investigated in further studies. We believe that this study provides an ideal foundation for further detailed investigation of important aspects that have been poorly studied so far. We now added "cross-sectional web-based survey" to the Methods section to clarify this and we clearly highlight the descriptive intent.

b. Can the title please be written in a non-declamatory voice and give the study design

We now changed the title and included the study design as "results from an international web-based survey".

e. Can there please be a sample size section - all studies need a sample size justification not all studies need a sample size calculation. This sample size justification can be narrative

We included a narrative sentence about the sample size calculation as follows: "No formal sample size calculation was made; a target sample size of >800 participants (with no allowance for multiplicity) was considered adequate." Following discussion with the co-author group, we arbitrary chose to aim for at least 800 participants, reflecting our goal of a broad and large sample.

f. Was the study impacted by COVID? If so can you please discuss the impact

This is an important point raised by the reviewer. The study was not impacted by COVID-19, and in fact represents a new alternative method for conducting studies in rare diseases at times of COVID-19, and potentially other global health care crises.

g. Can you please describe the outcomes for the study

A new section with outcomes has been added to the Methods.

h. For me personally one question asking to rate 1-10 I would say is quality of life outcome!

Outcomes, as indicated by the reviewer, were assessed on a visual analogue scale ranging from 0=no/minimum to 10=extreme/maximum. Outcomes such as diagnostic test burden, knowledge about cDI among physicians, different psychological characteristics were collected in this fashion. These outcomes are now mentioned in the methods section.

i. Have provided the overall date for the survey but can you please provide the dates for first physician, second newsletter and third twitter.

Physicians contacted patients on a regular base without any specific date restriction. The newsletters were dated 28.10.2021 (Pituitary World News), 17.12.2021 (Pituitary Foundation), 13.12.2021 (Twitter; Pituitary Society), and 20.10.2021 (Facebook Group 'Got diabetes insipidus'). This information is now included to the Methods section.

2. Can you please complete the STROBE checklist for abstracts (it is for conferences)

We completed and uploaded the STROBE checklist accordingly.

a. At the moment there are too many results quoted and should be cut down a little.

*We have shortened the results section and removed the "**breastfeeding section**" completely from the revised manuscript, as has also been suggested by another reviewer.*

b. As sated quoting all results can you please quote confidence intervals for prevalence data.
Prevalence data are now quoted with 95% confidence intervals as suggested.

c. Can you please be cautious in your conclusions "clear desire" term is not used in the main paper
We have corrected the abstract accordingly, and now used "support" as in the main paper.

3. For the survey can you please review and apply the CROSS checklist as appropriate (will lead authors to decide to complete) (https://www.equator-network.org/reporting-guidelines/a-consensus-based-checklist-for-reporting-of-survey-studies-cross/). It links to a paper and the checklist is in a table in the supplemental material in Supplemental 3

a. Sorry to swamp you with checklists. This one does overlap with STROBE. The items can be in the main paper or in the supplemental as appropriate. If you can please liaise with the editors if you can not get this paper
We thank the reviewer for providing the link to the CROSS checklist. We have completed the form and included the file with the supplementary material. We also mentioned the reporting with the CROSS checklist in the methods section.

b. Can the questionnaire please be provided in supplemental or links to them - there is the CRF in supplemental but this does not seam to map to a survey
The survey was not a one-page online form, instead an online version that switched from one question to the next and could only be continued if the previous question was answered. The questions were uploaded as a CRF, as correctly mentioned by the reviewer, and included all the items that were collected. All analyses were carried out from these collected data.

c. Did you have a child specific one - minus questions on sexual arousal?
There was no child-specific version, but the option skip questions, if not appropriate, e.g., sexual arousal.
We did, however, provide two sex-specific versions, i.e., males were not asked about gynaecological aspects.

d. In the paper can more detail please be decided on the methods just for the sampling procedures for the selection of people to be in the study
We have added a new section describing the method of sampling procedure (the active and passive recruitment steps in detail; included in the supplementary, p2-3) of patients with central diabetes insipidus as unselectively as possible, regardless of pre-specified eligibility criteria. The aim of this approach was to include a heterogeneous cohort of patients with central diabetes insipidus.

i. How were subjected identified?
All collaborators are experts in specialised centres who have access to large cohorts of patients with central diabetes insipidus that they either follow-up regularly in their clinics or have included in previous studies. In addition, patient associations which have a considerable network of a heterogeneous group of patients with central diabetes insipidus (e.g., Pituitary Foundation) were also involved in the recruitment process. Patients with rare diseases tend to exchange experiences through specialised forums – therefore, the recruitment also involved patient representatives with direct access to a global network of patients, e.g., via Facebook groups or Twitter (see below). This is now described in more detail (see supplementary, p2-3).

ii. How many and what attempts were made to contact them?
Patients were either actively contacted once (e.g., via direct contact in routine clinic reviews or by phone and e-mail) or the link was provided passively via the sources mentioned in the Methods section. The active and passive recruitment strategy is now described in more detail, see supplementary p2.

iii. Where were they approached?
To reach a high number of global participants recruitment was done in several ways:
First, physicians involved in this project informed patients with cDI by phone/e-mail or directly during routine clinic visits or hospitalisations about this voluntary anonymous survey and shared the link to the

homepage. In addition, patients waiting in the waiting-room were provided with QR-codes with direct access to the survey.
Second, announcements were shared in the Pituitary Foundation and Pituitary Worlds News homepage with a short description and direct link to the survey.
Third, social media, such as the globally active Facebook patient group 'Got diabetes insipidus?' and the Twitter account of the Pituitary Society, shared a short description and link to the survey.

iv. How did those who agree differ from those that did not (will revisit)?
Unfortunately, due to the anonymity of the survey, we cannot distinguish those who actively responded to our contact (provided via several sources as described in 2.d.iii) and participated from those who did not. This is a potential limitation of the study. Nonetheless, we anticipate that the large number of participants has probably ameliorated the impact of this point on our results.

e. How was informed consent obtained?
Patients visiting our homepage were first provided with information about the survey and its purpose and second, they could as well see all collaborators with affiliation. After actively continuing to the survey part by clicking, patients or their legal representative were informed about the anonymity of the data collection, and that by consenting to participate, the data would be processed, analysed, and published for research purposes, prior to the start of the survey. If consented, patients could start the survey by actively continuing by a click on the START button.

f. Can you please give the response rates and completion rates for those who start the survey (see comments later on missing data)
The survey was designed in a way that patients could continue it only if they had completely answered the previous question. Patients could also pause the survey and continue at a later time. We thus only received and analysed completed surveys - there were only 4 responses in the system that could not be analysed due to technical problems. Therefore, in this analysis only complete cases were saved, and a response or completion rate cannot be calculated. We have added this to the limitation section.

4. As eSurvey can you please review the CHERRIES checklist and apply as appropriate to the study for reporting. Will leave to authors discretion to complete and provide.

a. The CROSS paper says it incorporates CHERRIES but this one refers to IP addresses and cookies. Authors may wish to complete as have addressed these points
We have completed the CHERRIES and included them to the supplementary. We also mentioned the reporting with the CHERRIES checklist in the methods section.

5. For the statistical analyse
a. Can the methods for the prevalence ratios please be described.
We reported prevalences and odds ratios - no prevalence ratio was reported in our manuscript.

b. For the age categories would it make sense to add more categories for age?
Since no major sex and age specific differences could be observed in our analyses, we would prefer to keep the proposed age categories as they are for reasons of simplicity.

c. Do you have any data one what the overall population age and sex profile would be?
*From our own expertise and according to ORPHANNET (*www.orpha.net*) no sex differences are present, and the onset of the condition is around the age of 20; however, depending on the aetiology of diabetes insipidus the onset can vary from early childhood to later years of life. According to our data, the onset of the condition in our cohort is around 30 years.*

d. For the physician contacted patients do you have data on those approached who did not take part
Due to anonymity, we were not allowed to follow-up on the response rate of the contacted patients. We have added this to the limitation section.

e. Ideally when doing a survey it is good practice to apply the methods for population adjustment - the weighting - to allow for the sampling please be described
We unfortunately have no information on, for example, ethnicity, health care details, medications and comorbidities - and other variables - that in our view would be required for an adequate weighted analysis. Please note that the relationship of such characteristics with the survey outcomes/responses is not yet well understood, which would introduce considerable uncertainty to a weighted analysis.
We therefore decided to report the unadjusted results, fully acknowledging this limitation and we added this issue as limitation, following the reviewers' advice (please see next comment).

i. I note above responses to vary by age, sex and/or education
We agree with the reviewer and have commented to this in 1.d.iii.

ii. If can not weight can you please state as a limitation
We added this as a limitation, following the reviewers' advice.

f. Can there please be a statement that there is no allowance for multiplicity
The statement is included to the methods section.

g. Can it please be described how missing data were accommodated in the paper
See comment to point 3.f. We describe this now in more detail in the supplementary, see p4.

i. I assume there is missing data and so can there please be discussion on the sources of missing data and the extent of it
We included a detailed description about the technical design to avoid missing data in the supplementary (see supplementary, p4).

ii. There needs to be discussion as to the bias introduced by the missingness.
See comments on points 3.f and 4.g.ii.

iii. How many patients completed the questionnaire
Our server saved 1038 respondents, of whom 4 entries could not been included to the analysis due to technical problems. In total, 1034 patients completed the survey.

iv. Could provide more detailed tables in supplemental to show if non-responders (if possible)
No data about non-responders were collected, see above.

v. Did you consider imputation as sensitivity analyses?
No missing data were recorded, and no data imputation was foreseen therefore, see above.

h. Can the data handling procedures pleas be described. Including the database used and how the data were entered.
The data management was supported and provided by the IT team of the Department of Clinical Research, University Hospital Basel, Switzerland. The survey was hosted from one server and the data were saved on the MySQL-database; for the investigators the backend view Directus (directus.io) was used. As mentioned in the methods section, multiple-choice and (only few) open-ended questions were computed. By selecting the predefined multiple-choices of answers or entering the free-text and continuing to the next question, data were directly saved in the server of the University Hospital Basel. This technical method was chosen to avoid transfer errors between the survey platform and database. This is now described in more detail (see supplementary, p4).

i. For the logistical regression did you not consider covariates?
From a medical point of view, no other covariates (from the collected variables) are needed to be included in the model, since the outcome of hyponatraemia is a direct result of desmopressin therapy. Also, in previous

studies (see reference Behan LA et al. 2015) the same approach in reporting dysnatraemia prevalence was followed.

6. For Tables and Figures

a. Can there please be a study flow diagram to show the disposition of the people
i. This can show total people approached, responded, completed etc
No formal study flow diagram (with screening data, response rates, drop-outs) can be provided since only the available full dataset with no missing data was used for the analysis. We added this to the limitations section.

ii. Could show responses by approximate sources (please see comment above about dates for recruitment)
Unfortunately, we cannot answer this question with certainty because, in addition to the dates of recruitment as mentioned in 1.h.i., all collaborators have recruited independently of each other.

b. Can you please provide a table of the OR results. I would have in the main paper but this can be in supplemental.
We included the OR results in the supplemental material as requested. See p13.

c. For Table 1

i. Please see my comment on age categories
In Table 1, we divided between the two main age categories (children & adolescents / adults). The two main age categories for Table 1 are suggested for simplicity and comparison reasons with available studies.

ii. Do you have data as ethnicity
No data collection about ethnicity was allowed due to anonymity reasons.

iii. Could you add underlying conditions and medications (if to have Tables for Figures 1 to 3 can park this comment)
We aimed to design the questionnaire with as many questions as needed to answer our most urgent points. At the same time, we were keen to avoid overloading it with further questions, so that we have as many questionnaires completed and returned as possible.
We therefore unfortunately did not collect data on comorbidities (except anterior pituitary deficiencies) and medications (except desmopressin).

iv. Unclear why pooling age categories in the lower half of the paper
We corrected and divided the data according to both age categories in Table 1.

d. For Table 2
i. This would be informative to have 95 CI
We computed and included 95% confidence intervals as suggested.

e. For Table 3
ii. Please provide 95% CI for the contrasts
Table 3 is completely removed now from the revised manuscript. See comment to point 1.b.

iii. Please quote P-values up to 4 decimal places - if small can have P<0.0001
We corrected p-values according to the formatting guidelines.

iv. Please replace NS with P-values
Table 3 is completely removed now from the revised manuscript. See comment to point 1.b.

f. For Figures 1 to 3 and 4S
i. These personally I think would be better as Tables
To our knowledge, limited graphical representation about the aetiology, concomitant anterior hormone deficiency, and medication is available, and therefore these figures provide a simple data visualization.

*However, if the editor and reviewer wished, we would be happy to include the data into tables and remove the figures. We now included tables for **Figure 1** (-> Table 1S, supplementary p10), **Figure 2** (->see Results section, supplementary p6), **Figure 3** (->Table 2S, supplementary p11), **Figure 1S** (-> see Results section, supplementary p6).*

ii. 95% CI would be informative
We agree with the 95% CI suggestion and included accordingly (except for Table 1/Table 1S).

iii. I would replace the Figures with Tables but if to keep Figures then Tables need to be provided in supplemental
We now provided tables for Figure 1, 2, and 3 in the supplemental material.

iv. For 4S the y-axes need to be on the same scale i.e., 0 to 200
We corrected the y-axis as suggested.

Other comments
7. Is there a study protocol? If so can it please be provided or other documentation
As described in the methods section, a short proposal with the CRF of this survey was submitted to the local ethics committee, Ethical Committee Northwest and Central Switzerland. The ethical committee confirmed that a research project conducted with anonymous health-related personal data does not fall within the scope of the Swiss Human Research Act and therefore study conduct permission was granted. The questions of the survey were prespecified and remained unchanged through the conduct of the study. No detailed study protocol was used. However, all outcomes were described in the proposal as listed in the CRF. We now clearly state this in the supplemental material.

8. Is there a statistical analysis plan specific to this paper? If so can it please be provided.
Please see response before.

9. Can the reference for the ethics approval please be provided
We have uploaded a statement of our local ethics committee, Ethical Committee Northwest and Central Switzerland. As mentioned in point 8., a research project conducted with anonymous health-related personal data does not fall within the scope of the Swiss Human Research Act – the corresponding legal framework can be accessed via the following link: 810.30 Federal Act of 30 September 2011 on Research involving Human Beings (Human Research Act, HRA) https://www.fedlex.admin.ch/eli/cc/2013/617/en#chap_1

Edits
10. Could use a non-breaking hyphen for words like health-related
We corrected accordingly.

11. Can a data last access please be provided to web references
Data last access is included to the web reference.

Reviewer #4:

The authors, all experts in the field, have conducted a large survey in 1034 patients using a customized questionnaire developed by endocrinologists and patient representatives to assess the management of Central diabetes insipidus, the evaluation of psychological comorbidities, and level of awareness amongst healthcare professionals.

The results indicate a high rate of desmopressin-induced hyponatremia leading to hospitalization, high numbers of patients with mismanagement of their condition during hospitalization, and high prevalence of psychological co-morbidities including anxiety, depressed mood, and reduced QoL.

The main drawback belongs to the survey methodology, patient's selection bias, self-reported questionnaire and conclusions that lead to the request for renaming this condition. The fact that most patients have encountered a situation where central diabetes insipidus has been confused with "diabetes mellitus" by medical professionals and for this they advocate renaming the condition to avoid this confusion represent the patient's opinion and is questionable due to the lack of confirmation within a questionnaire from healthcare professionals who have managed patients with this condition. We're assuming that most physicians and healthcare professionals are unfamiliar with central diabetes insipidus and how to manage it.

We agree with the reviewer that patient's selection bias may be one of the limitations of this study. This is now mentioned in the limitations section of the revised manuscript (page 20); however, all participating collaborators contacted unselected patients to collect data of a cohort that would be as representative as possible of the general population of central diabetes insipidus. Our approach allowed us to include a very large sample and we assume that it reflects the views of patients, but we cannot rule out that selection bias affected our findings; however, we used a broad recruitment strategy, through social media, online dissemination, and personal contacts, and all actively recruited patients were contacted without any pre-specified eligibility criteria.

We also agree with the reviewer that a survey in medical personnel would be very interesting and would give some clarity about the awareness and management of patients with diabetes insipidus. This point has now been addressed in the discussion (see lines 646-647, page 19).

I support "We Should Leave No Stone Unturned" concept for patient safety, but before changing the name introduced in 1794 by Johann Peter Frank the reasons behind the need to move towards renaming central diabetes insipidus as a condition caused by "vasopressin deficiency or" AVP deficiency "deserve careful consideration.

Is really the word "diabetes" the main problem for patients with diabetes insipidus or lack of awareness? The main concern is that the general population, the press, and many healthcare professionals are primarily aware of diabetes mellitus? This is reasonable given the different prevalence of the condition, but it is precisely this inadequate of knowledge that puts patients with diabetes insipidus at risk.

What about patients with Wolfram disease or cancer survivors from hypothalamic-pituitary tumors and glucose metabolism imbalance living with both conditions i.e., diabetes mellitus and diabetes insipidus.?, and what about "Nephrogenic diabetes insipidus"……?

We agree with the reviewer that one of the driving factors for the confusion of diabetes insipidus and diabetes mellitus is the lack of knowledge about the condition. As mentioned by the reviewer, the difference in prevalence might here be the main reason.

The (fortunately few) case reports where this confusion has led to fatal outcomes, together with the high percentage of patients who seem to suffer from the confusion with diabetes mellitus, underline in our eyes the importance of re-thinking the naming of diabetes insipidus. This should clearly happen in a structured and well thought way, including not only endocrinologists, but also nephrologists (in order to address the problem of nephrogenic diabetes insipidus, as mentioned by the reviewer) and also including paediatricians and patient representatives.

A little of "Romanticism" in Medicine is mandatory by browsing some historical aspects starting from when the disease was already known in ancient Egypt, Greece and Asia until 1670 when Thomas Willis noticed the difference in the taste of urine subjects with polyuria compared to healthy individuals (the Arabs discovered it many years earlier), to Johann Peter Frank (1974), Farini (1913) who successfully used extracts of the posterior pituitary to treat Diabetes Insipidus up to more recent discoveries by others .

Having said that, why don't we change the name to diabetes mellitus by renaming it "Insulin deficiency"?. To my very personal view, changing the name of diabetes insipidus based on the above arguments looks merely esthetic.
We agree that the term "diabetes insipidus" as a medical term is a precise descriptive nomenclature. As mentioned above, a name change has to be thoroughly thought through and has to be performed in a structured way. An international working group is currently bringing together representatives of the main endocrine societies worldwide, as well as a representative of the nephrologist and paediatric societies in order to take on and discuss this challenging task.

The lack of reported nonresponse rate, dropout rate, item nonresponse rate represents a potential bias of consistency in validation. There is no consensus on acceptable minimum survey response rate, although acceptable rate has been reported from 40% to 75% across different specialties and the JAMA requires at least a 60% response rate.
The survey was designed in a way that patients could only continue the survey if they had completely answered the previous question. Patients could also pause the survey and continue at a later time. We thus only received and analysed complete surveys - there were only 4 responses in the system that could not be analysed due to technical problems.
Due to anonymity, we were not allowed to follow-up on the response rate of the contacted patients. We believe that with the high number of patients, the participation rate must be above 70% of those who were actively contacted though for the reasons mentioned above we are not able to prove this percentage.

Apart from the patients contacted by the physicians involved in the study, it is not clear how many and who are the respondents to the questionnaire worldwide. In addition, the breakdown according to the type of health systems involved and their differences is not shown. Therefore, it is not possible to assess the quality of the survey-based study. In addition, 80% of adult patients were women. This could affect the quality of life and psychological outcomes of the study.
We thank the reviewer for raising these important points.
Indeed, due to anonymity it is difficult to draw conclusions about different healthcare systems.
In addition, as correctly mentioned by the reviewer, a rate of 80% does not reflect the sex distribution in patients with diabetes insipidus. We know from numerous patient-reported outcome studies in different medical fields, that the response rate in females is generally higher compared to men. Interestingly, however, we show that despite the high proportion of females, there is no group difference in terms of psychological outcomes and quality of life (see supplementary Table 3S, p12), and hyponatremia rate (see response to reviewer 1). These points are now mentioned as limitation of our manuscript (lines 686-689, page 20).

Most of the patients (84%, n=869) think that physicians in general (e.g., during routine or emergency hospital admissions) have insufficient understanding of cDI and rated the general knowledge of physicians (not involved in the regular treatment of their cDI) with two out of ten possible VAS points. What should be acceptable as "insufficient" or "sufficient" knowledge? It seems that respondents' perception of the burden is more important than the burden itself.
This is an important point. Based on the results of this survey more detailed and qualitative interviews with patients and physicians should be performed to assess what "sufficient" knowledge about diabetes insipidus is (i.e., which specific points for management of the disease should be known by the different healthcare professionals).

I'm puzzled about the high prevalence of psychological co-morbidities IRRESPECTIVE of concomitant anterior pituitary hormone dysfunction. In this study, a high number of patients.
Self-reported bias that failed to identify the major psychological burden related to anterior pituitary defects is highly suspected. Table 1 and Figures 1 and 2 showed that patients with APD associated with central diabetes insipidus account for more than 50% and most of them have pituitary tumors or cysts. It remains difficult to capture and balance the psychological impact based on isolated diabetes insipidus rather than multiple pituitary defects associated with diabetes insipidus.
We refer to our answer to the next question about sexual arousal (see below). However, indeed, more data on psychological comorbidities in patients with isolated diabetes insipidus and on possible reasons are urgently needed.

Do the authors have any explanation for why sexual arousal was not different between patients with multiple pituitary defect including more than 300 patients with hypogonadism and those with isolated vasopressin deficiency?

*This is again a very important comment raised by the reviewer. Please also see our answer to **reviewer 1**.*
As reviewer 1 also mentioned, there is increasing evidence, primarily from animal experiments, that patients with diabetes insipidus may be at high risk for an additional oxytocin deficiency and this may at least partly explain sexual dysfunction and lower quality of life/ psychological burden. There is urgent need for more data about a possible oxytocin deficiency in humans with central diabetes insipidus.
*A recently published review nicely summarizes the hypothesis (**REF**. Clarke L, Zyga O, Pineo-Cavanaugh PL, et al. Socio-behavioral dysfunction in disorders of hypothalamic-pituitary involvement: The potential role of disease-induced oxytocin and vasopressin signaling deficits. Neurosci Biobehav Rev. 2022:104770.)*

How many questionnaires were filled by the patients and how many by the parents in the age group <18 years?

Regrettably, we did not collect this information.

"Desmopressin escape" is not the standard way to manage children or adolescents with central diabetes insipidus. Therefore, the analysis of these data should be stratified by age <18 years versus the others.

Thank you for this question. As suggested, we stratified the results by age:

Patients at the age of ≥18

The hyponatraemia prevalence in adults was 23% (95%-CI [0·19-0·26]; n=138/607) in patients performing desmopressin escape, 34% (95%-CI [0·27-0·40]; n=63/188) in those not aware of desmopressin escape, and 41% (95%-CI [0·32-0·51]; n=45/109) in patients aware of desmopressin escape but not using this method. Patients performing desmopressin escape had a significantly lower prevalence of hyponatraemia compared to those not being aware of this method (OR 0·58; 95%-CI [0·41-0·84]; p=0·0032) and to those aware of desmopressin escape but not using this method (OR 0·42; 95%-CI [0·27-0·64]; p<0·0001).

Patients at the age of <18

The hyponatraemia prevalence in children/adolescents was 12% (95%-CI [0·04-0·20]; n=7/60) in patients performing desmopressin escape, 35% (95%-CI [0·13-0·58]; n=6/17) in those not aware of desmopressin escape, and 8% (95%-CI [0·00-0·22]; n=1/13) in patients aware of desmopressin escape but not using this method. Patients performing desmopressin escape had a significantly lower prevalence of hyponatraemia compared to those not being aware of this method (OR 0·24; 95%-CI [0·07-0·88]; p=0·0285); however, not to those aware of desmopressin escape but not using this method (OR 1·58; 95%-CI [0·25-31·07]; p=0·6800).

We included this result in the supplemental material (see p7) and referred to it in the manuscript accordingly (see line 257, page 13).

Reviewer #5:
In this paper, the authors report data on psychological and quality of life and other parameters in a large number of patients with central DI using a web-based questionnaire.

1. Line 206. Minor point. The pituitary deficiencies really should be listed as TSH, ACTH and LH/FSH (or gonadotropin) rather than the replacement hormone. And in Fig. 2, the Thyroxine and Cortisol and Sex hormones could be deleted. Again, in the text, the same approach should be used (lines 205-206, 313).
We thank the reviewer for this comment and corrected; this section is now moved to the supplemental material. See supplementary p6, and Figure 2)

2. Line 371-375. Minor point. Break up this long sentence into 3 sentences.
We thank the reviewer for this useful suggestion that should improve readability.

Reviewer #6:

The article "Central diabetes insipidus from a patients' perspective: management, psychological co-morbidities, and re-naming of the condition" by Atila C et al. reports an interesting study performed on the results of a survey on 1034 patients with central DI (cDI). As cDI is very rare, and studies in real life of patients with this rare condition are scarce, the data provided by this study are very valuable and need to be reported.

Comments

1. This Reviewer understands that anonymity of data collection did not allow to trace the geographical repartition of the patients…and unfortunately the proportion of patients who responded to the questionnaire in each center. Thus, it is also difficult to know the proportion of patients followed in expert centers with high volume of patients versus non expert centers. Indeed, one important question is the representativeness of this study with regard to the general population of patients with DI. At least, are the Authors able to have an idea of the proportion of their patients who filled the questionnaire?

Unfortunately, due to anonymity of the survey, we are not able to answer this important question. The authors of the survey are all working in expert centres and the link was distributed through the pituitary society, pituitary world news, pituitary foundation etc. We assume that the majority of patients with central diabetes insipidus are managed in a specialized tertiary care center and only a minority in non-expert centers. We would also assume that patients managed in non-expert centres would experience even greater problems with treatment, general management of their disease, greater rate of hyponatraemia, and a higher rate of confusion with diabetes mellitus. We now mention this point of representativeness in the limitations section.

2. In the same line, one can assume that the questionnaire has been filled by the patients who were the most concerned with their DI, which may introduce a selection bias. This potential selection bias might be underlined as another limitation of the study.

We agree that selection bias may be one of the limitations of this study and we now mention and discuss this point on page 20; We, however, aim to mention that all participating collaborators contacted unselected patients to collect data in a cohort which should be as representative as possible. Of course, this is not always possible, please also see our answer to your question 1.

3. This is illustrated by the gender difference in the survey participants… the large (80%) proportion of female responders does not reflect, in the mind of this Reviewer, the population of the patients with DI… Do the Authors have an explanation?

As correctly mentioned by the reviewer, a rate of 80% does not reflect the sex distribution in patients with diabetes insipidus. Nevertheless, we know from numerous patient-reported outcome studies in different medical fields, that the response rate in females is generally higher compared to men. Interestingly, however, we found no indication for differences in terms of psychological outcomes and quality of life (see supplementary p12, Table 3S), and hyponatremia rate (see response to reviewer 1). This issue is now also mentioned in the revised manuscript.

4. Data on breastfeeding are too speculative and could be moved to Supplemental data.

We agree with the reviewer and now removed the complete section from the manuscript.

5. Maybe the article would gain in readability if it were shortened, some results being moved to supplemental data or their description reduced in the text and given in Tables. The same advice would also apply to Discussion.

As suggested by the reviewer, we shortened the results and discussion for better readability, and moved some parts to the supplemental material.

RESEARCH ARTICLE

Central diabetes insipidus from a patients' perspective: management, psychological co-morbidities, and re-naming of the condition - results from an international web-based survey

data from the DImond survey (Assessment of the characteristics of patients with central diabetes insipidus – from the diagnosis to the management of the condition)

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Short title: Patients' perspective on central diabetes insipidus

Keywords: diabetes insipidus; vasopressin; AVP deficiency; oxytocin; polyuria; polydipsia; dysnatraemia; hyponatraemia; hypernatraemia; psychological co-morbidities; safety; re-naming; desmopressin escape; breakthrough

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RESEARCH IN CONTEXT

Evidence before this study

Central diabetes insipidus (cDI) is a rare neuroendocrine condition resulting from arginine vasopressin (AVP) deficiency. Data about treatment-related side-effects, psychological co-morbidities, and prevalence of incorrect management due to lack of awareness among healthcare professionals are scarce. We searched PubMed up to March 01, 2022, for articles published in English, using the terms "diabetes insipidus", "desmopressin", "hyponatraemia", "hyponatremia", "hypernatraemia", "hypernatremia" "inpatient management", "safety", "psychological co-morbidities", "oxytocin", and "re-naming". Desmopressin, a vasopressin V2 receptor agonist, is the current standard of care in cDI. If patients are not correctly instructed on the use of desmopressin, even normal fluid intake can result in life-threatening hyponatraemia. Results from a retrospective study in 137 patients with cDI showed a 27% prevalence of mild and a 15% prevalence of profound hyponatraemia. The same study also demonstrated concerningly high rates of hypernatraemia, especially during hospital admissions, most likely as a result of inappropriate management. Owing to its rarity, cDI is a neglected condition among healthcare professionals; and occasional published case reports highlight the tragic and fatal consequences of treatment neglect during hospitalisation, which is partly explained by confusion with 'diabetes mellitus'(DM). These examples have given rise to an increasing interest in the potential need for re-naming cDI. In addition, only few attempts have been made to evaluate psychological co-morbidities and quality of life (QoL), especially in patients with isolated cDI. Limited available data demonstrate difficulties in emotion recognition, higher depression and anxiety symptoms compared to healthy controls despite adequate therapy with desmopressin.

Added value of this study

We conducted the largest survey to date in cDI using a customised questionnaire designed by medical professionals and patient involvement, hosted on a dedicated website. Our data indicate a high prevalence of desmopressin-induced hyponatraemia leading to hospitalisation. Patients instructed on the use of 'desmopressin escape', a method to omit or delay a desmopressin dose to allow intermittent aquaresis, showed a significantly lower prevalence of hyponatraemia compared to those not aware of

this approach. We also confirm concerningly high numbers of patients with mismanagement during hospitalisation: for example, around one in seven patients did not receive desmopressin (either orally or parenterally) while 'nil by mouth'/'nil per os' and did not receive intravenous fluid replacement and so reported symptoms of dehydration. The majority of patients encountered a situation where cDI was confused with DM by healthcare professionals, and 85% supported re-naming of the condition to avoid this confusion. We also report a high prevalence of psychological co-morbidities irrespective of concomitant anterior pituitary hormone dysfunction, especially heightened anxiety, depressed mood, and reduced QoL.

Implications of all the available evidence

The concerning numbers of mismanagement during hospitalisation and confusion with DM makes it imperative to provide healthcare professionals with more information about cDI and its management, and to ensure that desmopressin is recorded as an essential medication that must be available over the full 24h. Our data point to the importance of 'desmopressin escape' as a cost-free method resulting in lower prevalence of life-threatening hyponatraemia. Educating patients about this approach should be done when initiating desmopressin treatment with reminders when attending clinics. Further studies should investigate whether this approach then leads to lower risk of hyponatraemia.

In view of the prevalent psychological co-morbidities and reduced QoL shown in our study, future research is needed to investigate the psychopathological characteristics and possible treatment options in cDI. Re-naming of cDI, avoiding the word 'diabetes', would help ensure that cDI is recognised as requiring specialist life-sustaining therapy, which is distinct from DM. Such re-naming should be actively considered by members of the international endocrinology and internal medicine societies.

ABSTRACT

BACKGROUND Central diabetes insipidus (cDI) is a rare neuroendocrine condition. Data on treatment-related side-effects, psychological co-morbidities, and incorrect management are scarce. The aim of this survey was to investigate patients' perspectives on management and complications of cDI, psychological co-morbidities, patients' perspectives on the degree of knowledge and awareness of the condition amongst healthcare professionals, and views for re-naming cDI to avoid confusion with 'diabetes mellitus'(DM).

METHODS A cross-sectional web-based anonymous survey, developed by endocrinologists and patient representatives, assessing management of cDI, psychological co-morbidities, and level of awareness amongst healthcare professionals.

FINDINGS In total, 1034 patients with cDI participated, 47%(n=488) with isolated posterior and 53%(n=546) with combined anterior/posterior pituitary dysfunction. Main aetiologies were idiopathic 30%(n=315) and tumours/cysts (pre-surgical 21%(n=217), post-surgical 25%(n=254)).

Among patients on desmopressin therapy, 26%(95%-CI [0·24-0·29];n=273/994) experienced hyponatraemia leading to hospitalisation. Patients who routinely omitted/delayed desmopressin to allow intermittent aquaresis had a significantly lower prevalence of hyponatraemia compared to those not aware of this approach (OR 0·55; 95%-CI [0·39-0·77]; p=0·0006). During hospitalisation, around one in seven patients (95%-CI [0·10-0·16]; n=71/535) did not receive desmopressin while in a 'nil by mouth'/'nil per os' state without intravenous fluid replacement and reported symptoms of dehydration.

In total, 64%(95%-CI [0·61-0·67];n=660) reported lower quality of life and 36%(95%-CI [0·33-0·39];n=369) recognised psychological changes subjectively related to their cDI. Eighty percent (95%-CI [0·77-0·82];n=823) encountered a situation where cDI was confused with DM by healthcare professionals, and 85%(95%-CI [0·83-0·88];n=884) supported re-naming of the condition; the most favoured being 'vasopressin deficiency' or 'AVP deficiency'.

INTERPRETATION This is the largest survey of patients with cDI, reporting a high prevalence of treatment-related side-effects, mismanagement during hospitalisation, psychological co-morbidities,

and a clear support for re-naming the condition. Our data are the first to indicate the value of routinely omitting/delaying desmopressin.

FUNDING Swiss National Science Foundation; Swiss-Academy of Medical Sciences and G.&J.Bangerter-Rhyner-Foundation.

BACKGROUND

Central diabetes insipidus (cDI), a rare neuroendocrine condition with a prevalence of 1 in 25,000, is caused by arginine vasopressin (AVP) deficiency.(1) The condition is characterised by large volumes of unconcentrated urine, which are compensated by excessive fluid intake.(2) Once diagnosed, desmopressin, a selective vasopressin V2 receptor agonist, is usually prescribed to overcome the symptoms of polyuria, polydipsia, and nocturia.(3)

Data about desmopressin-related side-effects, insufficient awareness among medical professionals, and the prevalence of incorrect management of cDI are scarce and limited to small studies or case series. Occasional published case reports show the tragic and fatal consequences of treatment neglect with omission of desmopressin during hospitalisation, which is partly explained by confusion amongst healthcare professionals with 'diabetes mellitus'(DM).(4) These examples of mismanagement and confusion have given rise to increasing interest in the potential need for re-naming cDI, in order to avoid confusion with DM.

An enormous amount of research has been devoted to quality of life (QoL) in patients with anterior pituitary dysfunction (APD); however, in contrast, research covering QoL and psychological co-morbidities in patients with cDI has been limited. A few small studies have shown that even if patients are asymptomatic in terms of polyuria and polydipsia, psychological co-morbidities occur, with adverse effects on QoL, compared with healthy controls.(5, 6) However, important questions regarding psychopathological characteristics remain unanswered.

To address these issues, we conducted the largest study to date in patients with cDI, the 'DImond' survey (Assessment of the characteristics of patients with central diabetes insipidus – from the diagnosis to the management of the condition). This was a web-based survey, designed by patients and physicians, to investigate patients' perspectives on important issues, including: first, management and complications of cDI; second, psychological co-morbidities; third, patients' perspectives on the degree of knowledge and awareness of the condition amongst medical professionals; and fourth, enthusiasm for re-naming cDI to avoid confusion with DM.

METHODS

Design and participants

An anonymous cross-sectional web-based survey was conducted from 23.08.2021 to 07.02.2022 via the website of the Department of Clinical Research, University Hospital Basel, Switzerland. Patients with cDI were invited to participate in this voluntary 10-minute survey. The questions were developed by a multinational team of endocrinologists from Switzerland, the United Kingdom and Ireland, together with patient representatives from the United States. The survey consisted of eight sections with 35 main questions and was implemented as a custom web application supporting smartphones, tablets, and computers. Data were stored in a secured database of the University of Basel. Participant anonymity was ensured by hosting the application on internal servers, not using any external service providers or collecting identifying data (e.g., IP addresses or user-agent strings). Additionally, only strictly necessary client-side cookies were used. A random token was generated when the user navigated to the first question. This token was valid for a short period but lost its validity after submitting the survey, thus allowing users to complete the questionnaire even after the loss of internet connection or with temporary interruptions. Prior to the start of the survey, patients or their legal representative were informed about the anonymity of the data collection, and that by consenting to participate, the data would be processed, analysed, and published for research purposes (for details, see supplementary, p2-5). The proposal of this survey was submitted to the local ethics committee, Ethical Committee Northwest and Central Switzerland, who confirmed that a research project conducted with anonymous health-related personal data does not fall within the scope of the Swiss Human Research Act and therefore study conduct permission was granted. We used the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) and the Consensus-Based Checklist for Reporting of Survey Studies (CROSS) for reporting (see supplementary, p19).

Recruitment

Recruitment was done in several ways using different strategies and contact channels aiming for a large sample and reflecting the full spectrum of patients with cDI. First, physicians involved in this project informed patients with cDI by phone and directly during routine visits or hospitalisations about this

voluntary anonymous survey and shared the link to the homepage. Patients were contacted without any pre-specified eligibility criteria. Second, announcements were shared on websites of the *UK Pituitary Foundation* (date:28.10.2021) and *Pituitary Worlds News* (17.12.2021) with a description and direct link to the survey. Third, social media, such as the globally active Facebook patient group '*Got diabetes insipidus?*' (20.10.2021) and the Twitter account of *the Pituitary Society* (13.12.2021), shared a description and link to the survey. No formal sample size calculation was made; a target sample size of >800 participants (with no allowance for multiplicity) was considered adequate.

Objectives and outcomes

The objectives were to investigate patients' perspectives on management and complications as in- and out-patients, psychological co-morbidities, degree of knowledge and awareness among healthcare professionals, and views for re-naming cDI to avoid confusion with DM.

Outcomes were: first, occurrence and total number of hyponatraemic and hypernatraemic episodes since diagnosis, current and previous types and doses of desmopressin preparations, practice of intentionally delaying/omitting desmopressin dose to reduce the risk of hyponatraemia, occurrence of desmopressin access problems and episodes of withdrawal from desmopressin treatment while in a 'nil by mouth'/nil per os' state during hospitalisation; second, occurrence of psychological problems since diagnosis subjectively related to cDI (sub-domains: depressed mood, sleep disturbance, heightened anxiety, stress management disturbance, change in eating habits, change in personality), change in QoL subjectively related to cDI (sub-domains: social activities, recreation and fun, physical wellbeing, mental wellbeing), level of QoL, ability to trust others, social interaction, sexual arousal, anxiety level in general life using a 10-point scale; and third, confusion with DM by healthcare professionals and level of knowledge of physicians on cDI from a patients´ perspective on a 10-point scale. All questions are listed in the supplementary, p14.

Statistical analysis

All analyses were performed in *R* version 4·1·2 (2022-11-01). Discrete variables are expressed as frequencies (percentage (%) and number of patients (n)), continuous variables as median and interquartile range (IQR, 25^{th}-75^{th} percentiles). Patients <18 years of age are defined as

'children/adolescents' and ≥18 years of age are defined as 'adults'. Prevalence estimates are reported with 95% confidence intervals (CI), computed with the Wald Interval method. Data regarding the practice of delaying or omitting desmopressin dose until breakthrough symptoms (increased urinary frequency and strong thirst) occur to allow aquaresis, referred to by some as 'desmopressin escape' or 'water off-loading', was collected. In the following, we refer to this method as 'desmopressin escape'. A univariate logistic regression model was performed to describe the association of 'desmopressin escape' performance with the prevalence of hyponatraemia: patients aware of the 'desmopressin escape' method and following this approach were compared to patients aware of the need of 'desmopressin escape', but not following this approach, and to patients not aware of 'desmopressin escape' and not following this approach. We report odds ratios (OR) with 95%-CI. Qualitative measures (i.e., diagnostic test burden, knowledge about cDI among physicians, different psychological characteristics) were indicated on a visual analogue scale (VAS) ranging from 0 (no/minimum) to 10 (extreme/maximum). All analyses are exploratory and performed for the full dataset, patients with isolated posterior pituitary dysfunction, and patients with combined anterior/posterior pituitary dysfunction separately.

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

FINDINGS

In total, 1034 patients with cDI participated, 47%(n=488) with isolated posterior and 53%(n=546) with combined anterior/posterior pituitary dysfunction. The median [IQR] age in adults was 44 years [34-54] and 80% (n=757/943) were female; age in children/adolescents was 10 years [6-15] and 41% (n=37/91) were female. Median duration of cDI was 9 years [3-19] and the initial symptoms, i.e., polyuria 90%(n=930), polydipsia 88%(n=905), and nocturia 78%(n=810), began 0·3 years [0·1-1·0] prior to diagnosis. An initial diagnostic provocation test was performed in 58%(95%-CI [0·55-0·61]; n=602) (for details, see supplementary, p6). The aetiologies of cDI can be found in Figure 1, Table 1. Numbers of additional anterior pituitary hormone dysfunctions are reported in Figure 2, supplementary, p6.

Ninety-six percent (n=994) were on desmopressin therapy; of those, 56%(n=575) on oral tablets, 23%(n=233) on nasal sprays, 12%(n=126) on sub-lingual tablets, 3%(n=35) on a combination therapy (e.g., nasal spray plus oral tablets), 1%(n=14) on sub-cutaneous injections, and 1%(n=11) on rhinal tubes (Figure 3, supplementary, p11). For prevalences in switching types of preparation and availability of desmopressin in the local pharmacy, see supplementary, p6. The majority (95%, n=985) of patients indicated that they routinely saw a medical doctor twice [1-2] a year for reviews and check-ups of their cDI; 82%(n=857) an endocrinologist, 10%(n=99) a general practitioner, 2%(n=16) another specialist (e.g., oncologist), and 1%(n=13) a nephrologist.

'Desmopressin escape', a method to delay or omit a desmopressin dose to allow aquaresis, was performed by 67%(95%-CI [0·64-0·70]; n=667) of medicated patients: thirty-nine percent (95%-CI [0·36-0·42]; n=386) performed this approach daily, 16%(95%-CI [0·14-0·19]; n=160) several times a week, 12%(95%-CI [0·10-0·14]; n=121) once a week. Twenty-one percent (95%-CI [0·18-0·23]; n=205) of medicated patients were not aware of this approach, whilst 12%(95%-CI [0·10-0·14]; n=122) were aware, but did not use it.

In the out-patient setting, 22%(95%-CI [0·20-0·25]; n=230) (21%, 95%-CI [0·22-0·27]; n=211 in medicated patients) reported that they had experienced episodes of hyponatraemia, on a median of two occasions [2-4], with a similar incidence in adults and children/adolescents. The hyponatraemia prevalence was 17%(95%-CI [0·17-0·20]; n=114/667) in patients performing desmopressin escape, 32%(95%-CI [0·26-0·28]; n=65/205) in those not aware of desmopressin escape, and 26%(95%-CI [0·19-0·35]; n=32/122) in patients aware of desmopressin escape but not using this method. Patients performing desmopressin escape had a significantly lower hyponatraemia prevalence compared to those not being aware of this method (OR 0·44; 95%-CI [0·31-0·64]; p<0·0001) and to those aware of desmopressin escape but not using this method (OR 0·58; 95%-CI [0·37-0·92]; p=0·0178). There was no association between type of desmopressin preparation and hyponatraemia prevalence (for oral versus nasal spray, see supplementary, p13).

Overall, 35%(95%-CI [0·32-0·38]; n=364) reported an episode of dysnatraemia leading to hospital admission on at least one occasion. Twenty-six percent (95%-CI [0·24-0·29]; n=273) experienced

hyponatraemia on a median of two episodes [1-3] (27%; 95%-CI [0·25-0·30]; (n=259/943) in adults, 15%; 95%-CI [0·08-0·23]; (n=14/91) in children/adolescents). The hyponatraemia prevalence was 22%(95%-CI [0·18-0·25]; n=145/667) in patients performing desmopressin escape, 34%(95%-CI [0·27-0·40]; n=69/205) in those not aware of desmopressin escape, and 38%(95%-CI [0·29-0·46]; n=46/122) in those aware of desmopressin escape but not using this method. Similar to the findings in the out-patient setting, patients performing desmopressin escape had a significantly lower hyponatraemia prevalence leading to hospitalisation compared to those not aware of this method (OR 0·55; 95%-CI [0·39-0·77]; p=0·0006) and to those aware of desmopressin escape but not using this method (OR 0·46; 95%-CI [0·31-0·69]; p=0·0002)(for age stratification, see supplementary, p7).

Fifteen percent (95%-CI [0·12-0·17]; n=150) experienced hypernatraemia (14%; 95%-CI [0·11-0·16]; (n=128/943) in adults, 24%; 95%-CI [0·15-0·33]; (n=22/91) in children/adolescents), which occurred in each of these patients at a median of one episode [1-3]. Fifty-nine patients experienced episodes of both hypo- and hypernatraemia.

In total, 24%(95%-CI [0·21-0·26]; n=247) had problems accessing desmopressin during hospitalisation (e.g., for acute illness, elective surgery); among those, the most common reasons were non-availability of desmopressin (n=139), other reasons (e.g., desmopressin provided only on a scheduled time) (n=102), prescription of wrong dose (n=47) or complete lack of prescription (n=32).

Overall, 52%(95%-CI [0·49-0·55]; n=535) had to avoid eating and drinking for a medical reason during hospitalisations in elective (n=475) or emergency (n=150) situations. During this period, 54%(95%-CI [0·50-0·58]; n=290) received no intravenous fluids; of those, most of the patients used their own desmopressin (n=209) or desmopressin was given by the medical team (n=10); in contrast, one in seven (n=71) received no desmopressin, and these patients described classical symptoms of dehydration (e.g., ‘extreme thirst’, ‘dry eyes and mouth’, ‘nausea and shivering’).

Thirty-six percent (95%-CI [0·33-0·39]; n=369, equal prevalence in isolated posterior and combined pituitary dysfunction) experienced psychological problems, or recognised psychological changes subjectively related to their cDI: 25%(95%-CI [0·22-0·28]; n=258) reported heightened anxiety, 25%(95%-CI [0·23-0·28]; n=263) sleep disturbances, 23%(95%-CI [0·33-0·39]; n=239) depressed mood, 18%(95%-CI [0·15-0·20]; n=181) stress management disturbance, 16%(95%-CI [0·14-0·18]; n=168) change in eating habits, and 12%(95%-CI [0·10-0·14]; n=124) personality change (Table 2). Sixty-four percent (95%-CI [0·61-0·67]; n=660, equal prevalence in isolated posterior and combined pituitary dysfunction) reported lower QoL with six [4-7] out of ten VAS points, affecting social activities (n=538), recreation and fun (n=493), physical wellbeing (n=476), and mental wellbeing (n=414). Rates on a VAS regarding anxiety levels in general life, ability to build trust with others, ability in social interaction, and sexual arousal are presented in Table 2. The median rates were equal in isolated posterior and combined pituitary dysfunction with no major sex and age category specific differences (supplementary p12).

The majority (80%, 95%-CI [0·77-0·82]; n=823) indicated that healthcare professionals had confused their condition with DM on at least one occasion. Most of the patients (84%, 95%-CI [0·82-0·86]; n=869) think that physicians in general (e.g., during routine or emergency hospital admissions) have insufficient understanding of cDI and rated the general knowledge of physicians (not involved in the regular treatment of their cDI) with two [1-4] out of ten possible VAS points. Of those, 87%(95%-CI [0·84-0·89]; n=753) think that this lack of knowledge affected the management of their condition (e.g., repeated blood sugar measurements due to confusion). In total, 85%(95%-CI [0·83-0·88]; n=884) preferred a re-naming of the condition; amongst those, the most common suggestion was 'vasopressin deficiency' or 'AVP deficiency'. The one clear wish among all the comments was not to use the term 'diabetes' in the name of the condition.

INTERPRETATION

The data from our survey, the largest of its kind in patients with cDI, indicate a high prevalence of treatment-related side-effects leading to hospitalisation, particularly in patients unaware of the desmopressin escape approach, a high prevalence of psychological co-morbidities, a lack of knowledge and awareness of the condition amongst healthcare professionals, and strong support for re-naming the condition.

It is often not sufficiently recognised that many patients with rare illnesses such as cDI are experts on their conditions. The experiential knowledge that patients acquire after years of treatment is hard-won and unique, and deserves to be considered, both clinically and in research studies. Based on this consideration, this survey was developed and conducted by a team of expert endocrinologists together with patient representatives using a novel web-based method.

Most commonly, cDI results from acquired disruptions of the hypothalamic-pituitary axis, and less than 10% of the cases are hereditary.(7, 8) The spectrum of aetiologies of cDI indicated by our data are consistent with available literature, with hypothalamo-pituitary tumours or cysts as the most common cause of cDI (46%); however, there was a large proportion of idiopathic cases (30 to 50%), especially in isolated cDI.(7-9)

In anterior pituitary dysfunction (APD) it is usual that gonadotropins and growth hormone (GH) are more likely to be affected than adrenocorticotropin and thyroid-stimulating hormone (TSH). Our data appear to show discrepant results, with TSH as the most common concomitant hormone deficiency and GH as the least common. We speculate that the discrepant high incidence of hypothyroidism may reflect, in part, the high prevalence of primary hypothyroidism in idiopathic cDI,(10) and is probably not distinguished from secondary hypothyroidism by patients. In addition, not all adult patients with GH deficiency are tested for or receive GH replacement therapy, and may be unaware of their deficiency.

Desmopressin is the current standard of care for cDI. Our data show a clear preference for the oral route of desmopressin in those switching the type of preparation. A possible explanation is that alternative nasal preparations show great variability in effectiveness and switching to the oral route has been shown

to improve overall control.(11, 12) In contrast to the results of post-marketing safety data, which indicate a lower risk of hyponatraemia in oral compared to nasal desmopressin, (11, 12) our data showed a similar prevalence of patient-reported hyponatremia in patients with both preparations. Nonetheless, the use of oral preparations should be preferred, and well-designed studies are needed to further investigate this advantage. The antidiuretic effect of desmopressin can be affected by several factors such as solute intake and excretion, and fluctuating bioavailability (e.g., by nasal congestion for nasal sprays or concomitant food ingestion for oral route).(13) Despite this, patients often take a fixed dose at scheduled times. If not instructed on use of desmopressin escape, even normal daily fluid intake can result in water retention and development of hyponatraemia in the presence of sustained antidiuresis from rigid dose schedules. In the out-patient setting, a long-term follow-up study revealed a 27% of mild and a 15% prevalence of profound hyponatraemia.(14) In our study, patient-reported hyponatraemia was less frequent, suggesting that laboratory-confirmed hyponatraemia might even be higher. Our data also suggest a larger proportion of patients with hyponatraemia leading to hospitalisation. Desmopressin escape, a method to delay or omit desmopressin to allow aquaresis, has long been advised by some physicians to counteract this risk.(15) Our data are the first to demonstrate the value of this clinical approach, with lower prevalence of hyponatraemia in patients practising desmopressin escape. Patients who were instructed at initiation of desmopressin treatment, to delay or omit the dose once or more times a week had a lower prevalence of hyponatraemia. Hyponatraemia is particularly a complication in the out-patient setting,(14) and in the absence of patient education on hyponatraemia symptoms and desmopressin escape, it can quickly become life-threatening. In our opinion, this method should be instructed at every initiation of desmopressin therapy, as it is an approach resulting in immediate cost-free healthcare improvements i.e., reduced prevalence of life-threatening hyponatraemia and hospitalisation. Future prospective studies should investigate whether this method indeed leads to lower risk for hyponatraemia. Furthermore, in paediatric patients a more careful regimen is needed, and parents must be educated about hyponatraemia as a result of inappropriate management of desmopressin and fluid intake.(16)

Our data also show that a large number of patients (n=71) were unable to source desmopressin during hospitalisation when they were 'nil by mouth'/'nil per os' and without intravenous fluid replacement. Many of these patients reported symptoms of dehydration. Previously, Behan and colleagues reported concerningly high rates of hypernatraemia, particularly in in-hospital settings, most likely as a result of inappropriate management.(14) On the other hand, once admitted with hyponatraemia, physicians intuitively tend to discontinue desmopressin treatment.(17) This can lead to rapid overcorrection of serum sodium and result in severe neurological injury, if not appropriately monitored.(17) These findings points to the fact that the in-hospital management of patients should be led, or at least accompanied by, a specialist since patients with cDI are known to be highly vulnerable to rapid volume depletion in the context of severe illness if not adequately managed.(4, 18) Concern about mismanagement and delay of appropriate treatment led to a recent call for a campaign to increase awareness and education of medical personnel, and the request to include desmopressin as a high-alert medication with 24-h access in hospitals.(19) Consequently, the Society for Endocrinology UK published a clinical guidance covering the in-hospital management.(20)

Our data indicate a high prevalence of psychological co-morbidities in cDI, particularly heightened anxiety, depressed mood, sleeping difficulties, and lower sexual drives, consistent with small patient studies.(6, 21, 22) The patients also reported a reduced QoL, despite reduction of polyuria with desmopressin therapy. Impaired QoL and psychological changes in patients with APD are well recognised, and replacement therapy improves symptoms.(23, 24) In contrast, few attempts have been made to evaluate psychological co-morbidities in isolated cDI. The available data suggest that reduced QoL is partly explained by fluctuations in desmopressin efficacy, leading to changes in symptom control, or by concomitant pituitary hormone deficiencies.(5, 25, 26) Our data show that the reduction in QoL is equally apparent in isolated cDI and combined pituitary dysfunction, which challenges the assumption that concomitant pituitary hormone deficiencies are largely responsible.

Oxytocin (OT), the second neuropeptide released from the posterior pituitary, is known to mediate neuropsychiatric effects, including antidepressant, anxiolytic, and socioemotional functioning

properties, suggesting a potential role for OT deficiency in the increased psychopathology. This is supported by the results of a recent study.(6) Interestingly, one study reported that a single dose of intranasal OT improved emotion recognition in ten patients with craniopharyngioma and concomitant cDI. Conversely, in neuropsychiatric conditions intranasal OT has shown inconclusive results.(27) Future studies to investigate whether OT deficiency occurs in cDI, and whether treatment improves psychological symptoms, would be of interest.

According to National Health Service (NHS) England and the National Reporting and Learning System, 471 adverse incidents were reported from 2009 to 2015 involving desmopressin treatment.(4) Of these, prescription of the incorrect dose (*n*=56) and dose omission (*n*=76), were the most common errors. Tragically, four of these dose omissions resulted in death from severe dehydration.(4, 28) Consequently, the NHS sent an alert to all doctors informing them of the risk of omitting this life-sustaining medication.(4) In line with this, 24% of the patients in our survey reported problems accessing desmopressin during routine or emergency hospitalisations, most commonly due to non-availability. Owing to its rarity, cDI is a neglected condition among healthcare professionals, and increased awareness of this disease is urgently needed. In addition, cDI is often confused with DM. Patients in our survey indicated high rates of confusion with DM and insufficient understanding of cDI amongst healthcare professionals; both together can significantly increase the risk of mismanagement during hospitalisation, as indicated in this survey. Future survey studies could explore the knowledge of healthcare professionals on cDI and confirm the validity of the patient's perspective. Re-naming of cDI and avoiding the word ‘diabetes’ could help healthcare professionals understand that cDI requires specialist life-sustaining therapy, which is distinct from DM. Several patient representative associations and foundations strongly support this approach. The majority of patients suggested ‘AVP deficiency’ or ‘vasopressin deficiency’, and of particular importance for patients was not to use ‘diabetes’ in the name. For the nephrogenic form, ‘AVP resistance’ or ‘vasopressin resistance’ could be suggested.(29) A working group was recently set up by the main endocrine societies worldwide to discuss and propose alternative names for cDI.

The main limitation of the study is that due to the survey design we cannot make causal inferences. We have no control group from the general population or patients with isolated APD for comparison and no standardized longitudinal assessment of outcomes for patients with and without cDI. Since it was not our intent to assess causal effects, we did not use causal inference methods or adjust for confounding, and no weighting was performed. While there is, substantial data showing higher psychological co-morbidities in APD compared with the background population, psychological burden could be associated with the underlying disease. As our data indicate that lower QoL and psychological co-morbidities are comparable in patients with isolated DI and combined APD, it is reasonable to interpret our results as showing a higher psychological burden for patients with cDI than in the general population. The second main limitation is that due to the anonymous survey design, we have no empirical information on the representativeness of our very large sample. Our approach allowed us to include a very large sample and we assume that it reflects the views of patients, but we cannot rule out that selection bias affected our findings; however, we used a broad recruitment strategy, through social media, online dissemination, and personal contacts, and all actively recruited patients were contacted without any pre-specified eligibility criteria. In our survey, 77% of the participants were females and the impact on psychological outcomes is unclear; however, sex-stratification showed no major differences in our results. Third, also due to anonymity, response rates or differences according to each healthcare system could not be analysed. Finally, the reliability of self-reported data, especially for unawareness of hyponatraemia not leading to hospitalisation, the difficulty in interpreting potential anterior pituitary dysfunction such as hypothyroidism and GH deficiency, and the lack of information about other co-morbidities should be considered as a limitation. However, the outcomes of our survey are significant, objective events which patients most likely remember very well, limiting the potential impact of recall bias. In summary, our data underline the need to provide healthcare professionals with more information about cDI and its management, and to better educate patients about the strategy of desmopressin escape. More research is needed on the prevalence of psychological co-morbidities and possible treatment options in cDI. Furthermore, the re-naming of cDI should be actively considered by members of the international endocrinology societies.

Contributors

CA designed the questionnaire, which was then modified and refined with input from all authors, contributed to data collection, analysis, and interpretation, did the literature search, and wrote the manuscript. MCC edited the questionnaire, contributed to data analysis and data interpretation, edited the manuscript, and supervised all steps of the conduct of the study. LGH contributed to the data interpretation and edited the manuscript. All other co-authors contributed to data collection, contributed to data interpretation, and revised the manuscript. All authors had access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interest

We declare no competing interests.

Data sharing

We may share de-identified, individual participant-level data that underlie the results reported in this Article and related documents, including the study protocol and the statistical analysis plan. Data will be available with the publication of our main manuscript on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding author. The steering committee of this study will discuss all requests and decide based on the scientific rigor of the proposal whether data sharing is appropriate. All applicants are asked to sign a data access agreement.

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FIGURE CAPTIONS

Figure 1 Aetiologies of central diabetes insipidus

Bar plots represent each aetiology category's proportion for isolated central diabetes insipidus (cDI, in blue) and patients with combined central diabetes insipidus and anterior pituitary dysfunction (cDI & APD, in red).

Figure 2 Anterior pituitary dysfunction

Bar plots representing numbers of patients with combined central diabetes insipidus and anterior pituitary dysfunction in each category grouped according to the hormones. TSH= thyroid-stimulating hormone, ACTH= adrenocorticotropic hormone, LH/FSH= luteinizing hormone/follicle-stimulating hormone.

Figure 3 Type of desmopressin preparation

Bar plots represent the proportion of each desmopressin preparation. s.c. = subcutaneous.

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RESEARCH ARTICLE

Central diabetes insipidus from a patients' perspective:

management, psychological co-morbidities, and re-naming of the condition

- results from an international web-based survey

data from the DImond survey (Assessment of the characteristics of patients with central diabetes insipidus – from the diagnosis to the management of the condition)

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Short title: Patients' perspective on central diabetes insipidus

Keywords: diabetes insipidus; vasopressin; AVP deficiency; oxytocin; polyuria; polydipsia; dysnatraemia; hyponatraemia; hypernatraemia; psychological co-morbidities; safety; re-naming; desmopressin escape; breakthrough

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RESEARCH IN CONTEXT

Evidence before this study

Central diabetes insipidus (cDI) is a rare neuroendocrine condition resulting from arginine vasopressin (AVP) deficiency. Data about treatment-related side-effects, psychological co-morbidities, and prevalence of incorrect management due to lack of awareness among healthcare professionals are scarce. We searched PubMed up to March 01, 2022, for articles published in English, using the terms "diabetes insipidus", "desmopressin", "hyponatraemia", "hyponatremia", "hypernatraemia", "hypernatremia" "inpatient management", "safety", "psychological co-morbidities", "oxytocin", and "re-naming". Desmopressin, a vasopressin V2 receptor agonist, is the current standard of care in cDI. If patients are not correctly instructed on the use of desmopressin, even normal fluid intake can result in life-threatening hyponatraemia. Results from a retrospective study in 137 patients with cDI showed a 27% prevalence of mild and a 15% prevalence of profound hyponatraemia. The same study also demonstrated concerningly high rates of hypernatraemia, especially during hospital admissions, most likely as a result of inappropriate management. Owing to its rarity, cDI is a neglected condition among healthcare professionals; and occasional published case reports highlight the tragic and fatal consequences of treatment neglect during hospitalisation, which is partly explained by confusion with 'diabetes mellitus'-(DM). These examples have given rise to an increasing interest in the potential need for re-naming cDI. In addition, only few attempts have been made to evaluate psychological co-morbidities and quality of life (QoL), especially in patients with isolated cDI. Limited available data demonstrate difficulties in emotion recognition, higher depression and anxiety symptoms compared to healthy controls despite adequate therapy with desmopressin.

Added value of this study

We conducted the largest survey to date in cDI using a customised questionnaire designed by medical professionals and patient involvement, hosted on a dedicated website. Our data indicate a high ~~rate~~ prevalence of desmopressin-induced hyponatraemia leading to hospitalisation. Patients instructed on the use of 'desmopressin escape', a method to omit or delay a desmopressin dose to allow intermittent aquaresis, showed a significantly lower prevalence~~risk~~ of hyponatraemia compared to those not aware

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of this approach. We also confirm concerningly high numbers of patients with mismanagement during hospitalisation: for example, around one in seven patients did not receive desmopressin (either orally or parenterally) while 'nil by mouth'/'nil per os' and did not receive intravenous fluid replacement and so reported symptoms of dehydration. The majority of patients encountered a situation where cDI was confused with ~~'diabetes mellitus' (~~DM~~)~~ by healthcare ~~medical~~ professionals, and 85% supported re-naming of the condition to avoid this confusion. We also report a high prevalence of psychological co-morbidities irrespective of concomitant anterior pituitary hormone dysfunction, especially heightened anxiety, depressed mood, and reduced QoL.

Implications of all the available evidence

The concerning numbers of mismanagement during hospitalisation and confusion with DM makes it imperative to provide healthcare professionals with more information about cDI and its management, and to ensure that desmopressin is recorded as an essential medication that must be available over the full 24h. Our data point to the importance of 'desmopressin escape' as a cost-free method resulting in lower ~~risk~~ prevalence of life-threatening hyponatraemia. Educating patients about this approach should be done when initiating desmopressin treatment with reminders when attending clinics. Further ~~prospective~~ studies should investigate whether this approach then leads to lower ~~rates~~ risk of hyponatraemia.

In view of the prevalent psychological co-morbidities and reduced QoL shown in our study, future research is needed to investigate the psychopathological characteristics and possible treatment options in cDI. Re-naming of cDI, avoiding the word 'diabetes', would help ensure that cDI is recognised as requiring specialist life-sustaining therapy, which is distinct from DM. Such re-naming should be actively considered by members of the international endocrinology and internal medicine societies.

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ABSTRACT

BACKGROUND Central diabetes insipidus (cDI) is a rare neuroendocrine condition. Data on treatment-related side-effects, psychological co-morbidities, and incorrect management are scarce. The aim of this survey was to investigate patients' perspectives on management and complications of cDI, psychological co-morbidities, patients' perspectives on the degree of knowledge and awareness of the condition amongst healthcare professionals, and views for re-naming cDI to avoid confusion with 'diabetes mellitus'(DM).

METHODS A cross-sectional web-based anonymous survey, developed by endocrinologists and patient representatives, assessing management of cDI, psychological co-morbidities, and level of awareness amongst healthcare professionals.

FINDINGS In total, 1034 patients with cDI participated, 47%(n=488) with isolated posterior and 53%(n=546) with combined anterior/posterior pituitary dysfunction. Main aetiologies were idiopathic 30%(n=315) and tumours/cysts (pre-surgical 21%(n=217), post-surgical 25%(n=254)).

Among patients on desmopressin therapy, 26%(95%-CI [0·24-0·29];n=273/994) experienced hyponatraemia leading to hospitalisation. Patients who routinely omitted/delayed desmopressin to allow intermittent aquaresis had a significantly lower prevalence ~~risk~~ of hyponatraemia compared to those not aware of this approach (OR 0·55; 95%-CI [0·39-0·77]; p=0·0006~~p<0·01~~). During hospitalisation, around one in seven patients ~~1:7~~(95%-CI [0·10-0·16]; n=71/535) did not receive desmopressin while in a 'nil by mouth'/'nil per os' state without intravenous fluid replacement and reported symptoms of dehydration. In total, 64%(95%-CI [0·61-0·67];n=660) reported lower quality of life ~~QoL~~ and 36%(95%-CI [0·33-0·39];n=369) recognised psychological changes subjectively related to their cDI~~, most commonly 'heightened anxiety'~~. Eighty percent (95%-CI [0·77-0·82];n=823) encountered a situation where cDI was confused with ~~'diabetes mellitus'~~DM by healthcare professionals, and 85%(95%-CI [0·83-0·88];n=884) supported re-naming of the condition; the most favoured being 'vasopressin deficiency' or 'AVP deficiency'.

INTERPRETATION This is the largest survey of patients with cDI, reporting a high prevalence ~~rates~~ of treatment-related side-effects, mismanagement during hospitalisation, psychological co-morbidities,

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and a clear ~~preference~~ support for re-naming the condition. Our data are the first to ~~demonstrate~~ indicate the value of routinely omitting/delaying desmopressin.~~, to reduce risk of hyponatraemia.~~

FUNDING Swiss National Science Foundation; Swiss-Academy of Medical Sciences and G.&J.Bangerter-Rhyner-Foundation.

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BACKGROUND

Central diabetes insipidus (cDI), a rare neuroendocrine condition with a prevalence of 1 in 25,000, is caused by arginine vasopressin (AVP) deficiency.(1) The condition is characterised ~~clinically~~ by large volumes of unconcentrated urine, which are compensated by excessive fluid intake.(2) Once diagnosed, desmopressin, a selective vasopressin V2 receptor agonist, is usually prescribed to overcome the symptoms of polyuria, polydipsia, and nocturia.(3)

Data about desmopressin-related side-effects, insufficient awareness among medical professionals, and the prevalence of incorrect management of cDI are scarce~~,~~ and limited to small studies or case series. Occasional published case reports show the tragic and fatal consequences of treatment neglect with omission of desmopressin during hospitalisation, which is partly explained by confusion amongst healthcare professionals with 'diabetes mellitus'(DM).(4) These examples of mismanagement and confusion have given rise to ~~an~~ increasing interest in the potential need for re-naming cDI, in order to avoid confusion with DM.

An enormous amount of research has been devoted to quality of life (QoL) in patients with anterior pituitary dysfunction (APD); however, in contrast, research covering QoL and psychological co-morbidities in patients with cDI has been limited. A few small studies have shown that even if patients are asymptomatic in terms of polyuria and polydipsia, psychological co-morbidities occur, with adverse effects on QoL, compared with healthy controls.(5, 6)~~(5-8)~~ However, important questions regarding psychopathological characteristics remain unanswered.

To address these issues, we conducted the largest study to date in patients with cDI, the 'DI~~-~~mond' survey (Assessment of the characteristics of patients with central diabetes insipidus – from the diagnosis to the management of the condition). This was a web-based ~~questionnaire~~survey, designed by patients and physicians, to investigate patients' perspectives on important issues, including: first, management and complications of cDI; second, psychological co-morbidities; third, patients' perspectives on the degree of knowledge and awareness of the condition amongst medical professionals; and fourth, enthusiasm for re-naming cDI to avoid confusion with DM.

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METHODS

Design and participants

An anonymous cross-sectional web-based survey was conducted from 23.08.2021 ~~August 2021~~ to 07.02.2022 ~~February 2022~~ via the website of the Department of Clinical Research, University Hospital Basel, Switzerland. Patients with cDI were invited to participate in this voluntary 10-minute ~~online~~ survey. The questions were developed by a multinational team of endocrinologists from Switzerland, the United Kingdom~~,~~ and Ireland, together with patient representatives from the United States. The survey consisted of eight sections with 35 main questions and

~~The survey~~ was implemented as a custom web application supporting smartphones, tablets, and ~~desktop~~ computers. Data ~~collected in this survey~~ were stored in a secured database of the University of Basel. Participant anonymity was ensured by hosting the application on internal servers, ~~refraining from~~not using any external service providers or collecting identifying data (e.g.,~~, such as~~ IP addresses or user-agent strings). Additionally, only strictly necessary client-side cookies were used. A random token was generated when the user navigated to the first question. This token was valid for a short period but lost its validity after submitting the survey, thus allowing users to complete the questionnaire even after the loss of internet connection or with temporary interruptions. Prior to the start of the survey, patients or their legal representative were informed about the anonymity of the data collection, and that by consenting to participate, the data would be processed, analysed, and published for research purposes (~~f~~For ~~more~~ details ~~about survey methodology~~, see supplementary, p2-5).

The proposal of this survey was submitted to the local ethics committee, Ethical Committee Northwest and Central Switzerland, who confirmed that a research project conducted with anonymous health-related personal data does not fall within the scope of the Swiss Human Research Act and therefore study conduct permission was granted. We used the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) and ~~CROSS (~~the Consensus-Based Checklist for Reporting of Survey Studies (CROSS)~~)~~ for reporting (see supplementary, p19~~-~~).

Recruitment

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Recruitment was done in several ways~~,~~ using different strategies and contact channels aiming for a large sample and reflecting the full spectrum of patients with cDI. First, physicians involved in this project informed patients with cDI by phone and directly during routine visits or hospitalisations about this voluntary anonymous survey and shared the link to the homepage. Patients were contacted without any pre-specified eligibility criteria. Second, announcements were shared on websites of the *UK Pituitary Foundation (date:28.10.2021)* and *Pituitary Worlds News (17.12.2021)* ~~homepages~~ with a ~~short~~ description and direct link to the survey. Third, social media, such as the globally active Facebook patient group '*Got diabetes insipidus?*' *(20.10.2021)* and the Twitter account of *the Pituitary Society (13.12.2021),* shared a ~~short~~ description and link to the survey. No formal sample size calculation was made; a target sample size of >800 participants (with no allowance for multiplicity) was considered adequate.

Objectives and ~~data items~~

~~The survey included several multiple-choice and open-ended questions and was comprised of five sections: 'patient characteristics', 'management as in- and out-patients', 'psychological co-morbidities', 'breastfeeding', and 'knowledge and awareness among healthcare professionals and re-naming of cDI'.~~

~~All questions developed for this survey can be found in the supplemental material.~~ outcomes

The objectives were to investigate patients' perspectives on management and complications as in- and out-patients, psychological co-morbidities, degree of knowledge and awareness among healthcare professionals, and views for re-naming cDI to avoid confusion with DM.

Outcomes were: first, occurrence and total number of hyponatraemic and hypernatraemic episodes since diagnosis, current and previous types and doses of desmopressin preparation, practice of intentionally delaying/omitting desmopressin dose to reduce the risk of hyponatraemia, occurrence of desmopressin access problems ~~during hospitalisation,~~ and episodes of withdrawal from desmopressin treatment while in a 'nil by mouth'/nil per os' state during hospitalisation; second, occurrence of psychological problems since diagnosis subjectively related to cDI (sub-domains: depressed mood, sleep disturbance, heightened anxiety, stress management disturbance, change in eating habits, change in personality), change in QoL subjectively related to cDI (sub-domains: social activities, recreation and

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fun, physical wellbeing, mental wellbeing), level of QoL, ability to trust others, social interaction, sexual arousal, anxiety level in general life using a 10-point scale; and third, confusion with DM by healthcare professionals and level of knowledge of physicians on cDI from a patients' perspective on a 10-point scale. All questions are listed in the supplementary, p14.

Statistical analysis

All analyses were performed in *R* version 4·1·2 (2022-11-01~~10~~). Discrete variables are expressed as frequencies (percentage (%) and number of patients (n)), continuous variables as median and interquartile range (IQR, 25^{th} ~~to~~ 75^{th} percentiles). Patients <18 years of age are defined as 'children/adolescents' and ≥18 years of age are defined as 'adults'. P~~p~~revalence~~s~~ estimates are reported with 95% confidence intervals (CI)~~CI~~, computed ~~according to~~with the Wald Interval method. Data regarding the practice of delaying or omitting desmopressin dose until breakthrough symptoms (increased urinary frequency ~~increased frequency in urination~~ and strong thirst) occur to allow aquaresis, referred to by some as 'desmopressin escape' or 'water off-loading', was collected. In the following, we refer to this method as 'desmopressin escape'. A univariate logistic regression model was performed to ~~assess~~ describe the association of 'desmopressin escape' performance with the prevalence of~~on~~ hyponatraemia~~ risk~~: patients aware of the 'desmopressin escape' method and following this approach were compared to patients aware of the need of 'desmopressin escape', but not following this approach, and to patients not aware of 'desmopressin escape' and not following this approach. We report odds ratios (OR) with 95~~%~~ % ~~confidence intervals (~~CI~~)~~. Qualitative measures (i.e., diagnostic test burden, knowledge about cDI among physicians, different psychological characteristics) were indicated on a visual analogue scale (VAS) ranging from 0 (no/minimum) to 10 (extreme/maximum). ~~Proportion differences between female patients with isolated posterior versus combined anterior/posterior pituitary dysfunction in difficulties with breastfeeding were analysed using the Chi square test; p values <0·05 were considered statistically significant.~~ All ~~further~~ analyses are exploratory and performed for the ~~pooled~~ full data~~ set, the subgroups of~~ patients with isolated posterior pituitary dysfunction, and patients with combined anterior/posterior pituitary dysfunction separately.

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Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. ~~All authors had access to all the data and had final responsibility for the decision to submit for publication.~~

FINDINGS

~~Patient characteristics~~

In total, 1034 patients with cDI participated, 47%(n=488) with isolated posterior and 53%(n=546) with combined anterior/posterior pituitary dysfunction. The median [IQR] age in adults was 44 years [34-54] and 80% (n=757/943) were female; age in children/adolescents was 10 years [6-15] and 41% (n=37/91) were female. Median duration of cDI was 9 years [3-19] and the initial symptoms, i.e., polyuria 90%(n=930), polydipsia 88%(n=905), and nocturia 78%(n=810), began 0·3 years [0·1-1·0] prior to diagnosis. An initial diagnostic provocation test was performed in 58%(n=602) (for details, see supplementary, p6). ~~of those, most underwent the water deprivation test (n=578) with a test burden of eight [6-10] points out of ten on a VAS, followed by the hypertonic saline infusion test (n=45) with a burden of six [3-9] VAS points, and the arginine infusion test (n=35) with a burden of five [3-9] VAS points. Reasons for discomfort during the test were the long thirst phase (n=489), long test duration (n=327), side effects (e.g., nausea) (n=197), repeated blood sampling (n=192), and other reasons (e.g., inexperienced medical team) (n=110). The remaining patients (e.g., patients after pituitary surgery) without a provocation test indicated that their diagnosis was made according to physical examination, blood and urine laboratory assessments, and imaging of the brain and pituitary gland.~~ The aetiologies of cDI can be found in Figure 1, Table 1. Numbers of additional anterior pituitary hormone dysfunctions are ~~demonstrated~~ reported in Figure 2, supplementary, p6.

~~Patients with combined pituitary dysfunction indicated additional deficiencies i.e., thyroxine (n=421), cortisol (n=359), estrogen/testosterone (n=313), growth hormone (n=311), or excesses i.e., prolactinoma (n=68), Cushing's disease (n=42), and acromegaly (n=17) (Figure 2).~~

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~~Management as in- and out-patients~~

~~a) Medication with desmopressin and related side-effects~~

Ninety-six percent (n=994) were on desmopressin therapy; of those, 56%(n=575) on oral tablets, 23%(n=233) on nasal sprays, 12%(n=126) on sub-lingual tablets, 3%(n=35) on a combination therapy (e.g., nasal spray plus oral tablets), 1%(n=14) on sub-cutaneous injections, and 1%(n=11) on rhinal tubes (Figure 3, supplementary, p11~~Table 2~~4S). For ~~rates~~ prevalences in switching types of preparation and availability of desmopressin in the local pharmacy, see supplementary, p6~~3~~. ~~Overall, 38%(n=389) switched the type of preparation after diagnosis, most commonly from nasal sprays (n=209) to oral tablets (n=208), due to availability (n=147), personal preferences (n=134), doctors' recommendation (n=99), and side-effects (n=73) (supplementary Figure 4S). Half of the patients (46%, n=478) had encountered at least one occasion where they were unable to source their desmopressin in the local pharmacy.~~ The majority (95%, n=985) of patients indicated that they routinely saw a medical doctor twice [1-2] a year for reviews and check-ups of their cDI; 82%(n=857) an endocrinologist, 10%(n=99) a general practitioner, 2%(n=16) another specialist (e.g., oncologist), and 1%(n=13) a nephrologist.

'Desmopressin escape', a method to delay or omit a desmopressin dose to allow aquaresis, was performed by 67%(95%-CI [0·64-0·70]; n=667) of medicated patients: thirty-nine percent (95%-CI [0·36-0·42]; n=386) performed this approach ~~every day~~daily, 16%(95%-CI [0·14-0·19]; n=160) several times a week, 12%(95%-CI [0·10-0·14]; n=121) once a week. Twenty-one percent (95%-CI [0·18-0·23]; n=205) of medicated patients were not aware of this approach, whilst 12%(95%-CI [0·10-0·14]; n=122) were aware, but did not use it.

In the out-~~-~~patient setting, 22%(95%-CI [0·20-0·25]; n=230) (21%, 95%-CI [0·22-0·27]; n=211 in medicated patients) reported that they had experienced episodes of hyponatraemia, on a median of two occasions [2-4], with a similar incidence in adults and children/adolescents. The hyponatraemia prevalence ~~rate~~ was 17%(95%-CI [0·17-0·20]; n=114/667) in patients performing desmopressin escape, 32%(95%-CI [0·26-0·28]; n=65/205) in those not aware of desmopressin escape, and 26%(95%-CI [0·19-0·35]; n=32/122) in patients aware of desmopressin escape but not using this method. Patients performing desmopressin escape had a significantly lower ~~risk of~~ hyponatraemia prevalence compared

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to those not being aware of this method (OR 0·44; 95%-CI [0·31-0·64]; p<0·0001) and to those aware of desmopressin escape but not using this method (OR 0·58; 95%-CI [0·37-0·92]; p=0·0178). There was no association between ~~route of administration~~type of desmopressin preparation and hyponatraemia prevalence ~~risk~~ (for~~e.g.,~~ oral versus nasal spray,~~-~~ see supplementary, p13~~Table 5S, pXOR 1·22; 95% CI [0·74-2·07]; p=0·4520, analysed only for patients who did not switch the type of desmopressin~~).

~~**b) Hospital admission due to dysnatraemia (hyper- or hyponatraemia) and management during hospitalisation**~~

Overall, 35%(95%-CI [0·32-0·38]; n=364) reported an episode of dysnatraemia leading to hospital admission on at least one occasion. Twenty-six percent (95%-CI [0·24-0·29]; n=273) experienced hyponatraemia on a median of two episodes [1-3] (27%; 95%-CI [0·25-0·30]; (n=259/943) in adults, 15%; 95%-CI [0·08-0·23]; (n=14/91) in children/adolescents). The hyponatraemia prevalence ~~rate~~ was 22%(95%-CI [0·18-0·25]; n=145/667) in patients performing desmopressin escape, 34%(95%-CI [0·27-0·40]; n=69/205) in those not aware of desmopressin escape, and 38%(95%-CI [0·29-0·46]; n=46/122) in those aware of desmopressin escape but not using this method. Similar to the findings in the out-patient setting, patients performing desmopressin escape had a significantly lower ~~risk of~~ hyponatraemia prevalence leading to hospitalisation compared to those not aware of this method (OR 0·55; 95%-CI [0·39-0·77]; p=<0·00061) and to those aware of desmopressin escape but not using this method (OR 0·46; 95%-CI [0·31-0·69]; p=<0·00021)(for age stratification, see supplementary, p7~~age~~ ~~~~).

Fifteen percent (95%-CI [0·12-0·17]; n=150) experienced hypernatraemia (14%; 95%-CI [0·11-0·16]; (n=128/943) in adults, 24%; 95%-CI [0·15-0·33]; (n=22/91~~8~~) in children/adolescents), which occurred in each of these patients at a median of one episode [1-3]. Fifty-nine patients experienced episodes of both hypo- and hypernatraemia.

In total, 24%(95%-CI [0·21-0·26]; n=247) had problems accessing desmopressin during hospitalisation (e.g., for acute illness, elective surgery); among those, the most common reasons were non-availability of desmopressin (n=139), other reasons (e.g., desmopressin provided only on a scheduled time) (n=102), prescription of ~~a~~ wrong dose (n=47) or complete lack of prescription (n=32).

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Overall, 52%(95%-CI [0·49-0·55]; n=535) had to avoid eating and drinking for a medical reason during hospitalisations in elective (n=475) or emergency (n=150) situations. During this period, 54%(95%-CI [0·50-0·58]; n=290) received no intravenous fluids; of those, most of the patients used their own desmopressin (n=209) or desmopressin was given by the medical team (n=10); in contrast, one in seven (n=71) received no desmopressin, and these patients described classical symptoms of dehydration (e.g., 'extreme thirst', 'dry eyes and mouth', 'nausea and shivering') ~~and experienced extreme discomfort~~.

~~Psychological co-morbidities~~

Thirty-six percent (95%-CI [0·33-0·39]; n=369, equal prevalence in isolated posterior and combined pituitary dysfunction) experienced psychological problems, or recognised psychological changes subjectively related to their cDI~~ after the diagnosis~~: 25%(95%-CI [0·22-0·28]; n=258) reported heightened anxiety, 25%(95%-CI [0·23-0·28]; n=263) sleep disturbances, 23%(95%-CI [0·33-0·39]; n=239) depressed mood, 18%(95%-CI [0·15-0·20]; n=181) stress management disturbance, 16%(95%-CI [0·14-0·18]; n=168) change in eating habits, and 12%(95%-CI [0·10-0·14]; n=124) personality change (Table 2). Sixty-four percent (95%-CI [0·61-0·67]; n=660, equal prevalence in isolated posterior and combined pituitary dysfunction) reported lower QoL with six [4-7] out of ten VAS points, affecting social activities (n=538), recreation and fun (n=493), physical wellbeing (n=476), and mental wellbeing (n=414). Rates on a VAS regarding ~~Patients indicated their~~ anxiety levels in general life~~ with six [3-8] VAS points~~, ability to build trust with others~~ with seven [4-8] VAS points~~, ability in social interaction~~ and connection to others with seven [5-8] VAS points~~, and ~~rate in~~ sexual arousal are presented in ~~(answered by n=819) with three [2-7] VAS points (~~Table 2~~)~~. The median rates were equal in isolated posterior and combined pituitary dysfunction with no major sex and age category specific differences (supplementary p12~~Table S5~~).

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~~Breastfeeding~~

~~In total, 138 women (65% (n=90) with isolated cDI, 35%(n=48) with combined pituitary dysfunction) had given birth after the diagnosis of cDI. Overall, 18%(n=25) did not attempt to breastfeed and 30%(n=41) had no difficulties; 52%(n=72) had difficulties with breastfeeding, such as inability (n=41), low milk volume (n=35), short breastfeeding period (n=23), and pain (n=12). Patients with combined pituitary dysfunction had a higher rate of difficulties compared to patients with isolated cDI (69% versus 43%, p=0·01); in particular, a higher rate of low milk volume (50% versus 12%, p<0·01) (Table 3).~~

~~Knowledge and awareness of healthcare professionals and re-naming of the condition~~

The majority ~~of the patients~~ (80%, 95%-CI [0·77-0·82]; n=823) indicated that healthcare professionals had confused their condition with DM on at least one occasion. Most of the patients (84%, 95%-CI [0·82-0·86]; n=869) think that physicians in general (e.g., during routine or emergency hospital admissions) have insufficient understanding of cDI and rated the general knowledge of physicians (not involved in the regular treatment of their cDI) with two [1-4] out of ten possible VAS points. Of those, 87%(95%-CI [0·84-0·89]; n=753) think that this lack of knowledge affected the management of their condition (e.g., repeated blood sugar measurements due to confusion). In total, 85%(95%-CI [0·83-0·88]; n=884) preferred a re-naming of the condition; amongst those, the most common suggestion was 'vasopressin deficiency' or 'AVP deficiency'. The one clear wish among all the comments was not to use the term 'diabetes' in the name of the condition.

INTERPRETATION

The data from our survey, the largest of its kind in patients with cDI, indicate a high prevalence ~~proportion~~ of treatment-related side-effects leading to hospitalisation, particularly in patients unaware of the desmopressin escape approach, a high prevalence of psychological co-morbidities, a lack of knowledge and awareness of the condition amongst healthcare professionals, and strong support for re-naming the condition.

It is often not sufficiently recognised that many patients with rare illnesses such as cDI are experts on their conditions. The experiential knowledge that patients acquire after years of treatment is hard-won and unique, and deserves to be ~~taken into account~~considered, both clinically and in research studies. Based on this consideration, this survey was developed and conducted by a team of expert endocrinologists together with patient representatives using a novel web-based method.

Most commonly, cDI results from acquired disruptions of the hypothalamic-pituitary axis, and less than 10% of the cases are hereditary.(7, 8) The spectrum of aetiologies of cDI indicated by our data are consistent with available literature, with hypothalamo-pituitary tumours or cysts as the most common cause of cDI (46%); ~~there was,~~ however, there was a large proportion of idiopathic cases (30 to 50%), especially in isolated cDI.(7-9) ~~Data in the literature suggest that a majority of the idiopathic cases result from immunological causes, and the detection of specific antibodies (e.g., anti-rabphilin-3a in lymphocytic infundibuloneurohypophysitis and IgG4 in IgG4-related hypophysitis) might improve the diagnostic approach to 'idiopathic' cDI in the future; further studies are needed to investigate this in more detail.(10, 11)~~

In anterior pituitary dysfunction (APD) it is usual that gonadotropins and growth hormone (GH) are more likely to be affected than adrenocorticotropin and thyroid-stimulating hormone (TSH). Our data appear to show discrepant results, with TSH ~~thyroxine~~ as the most common concomitant hormone deficiency and GH as the least common. We speculate that the discrepant high incidence of hypothyroidism may reflect, in part, the high prevalence of primary hypothyroidism in idiopathic ~~diabetes insipidus~~cDI,(10) and is probably not distinguished from secondary hypothyroidism by patients. In addition, not all adult

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patients with GH deficiency are tested for or receive GH replacement therapy, and may be unaware of their deficiency.

Desmopressin is the current standard of care for cDI. Our data show a clear preference for the oral route of desmopressin in those switching ~~from one to another~~the type~~s~~ of preparation. A possible explanation is that ~~the~~ alternative nasal preparations show great variability in effectiveness and ~~the~~ switching to the oral route has been shown to improve overall control.(11, 12) In contrast to the results of post-marketing safety data, which indicate a lower risk of hyponatraemia in oral compared to nasal desmopressin preparations,(11, 12) our data showed a similar prevalence ~~rate~~ of patient~~self~~-reported hyponatremia in patients with ~~oral, compared to nasal~~both preparations. Nonetheless, the use of oral preparations should be preferred, and well-designed studies are needed to further investigate this advantage. The antidiuretic effect of desmopressin can be affected by several factors such as solute intake and excretion, and fluctuating bioavailability (e.g., by nasal congestion for nasal sprays or concomitant food ingestion for oral route).(13) ~~However, D~~despite this, patients often take a fixed dose at scheduled times. If not instructed on use of desmopressin escape, even normal daily fluid intake can result in water retention and development of hyponatraemia in the presence of sustained antidiuresis from rigid dose schedules. In the out-patient setting, a long-term follow-up study revealed a 27% of mild and a 15% ~~incidence~~ prevalence of profound hyponatraemia.(14) In our study, patient-reported hyponatraemia was less frequent, suggesting that laboratory-confirmed hyponatraemia might even be higher. Our data also suggest a larger proportion of patients with hyponatraemia leading to hospitalisation~~s~~. Desmopressin escape, a method to delay or omit desmopressin to allow aquaresis, has long been advised by some physicians to counteract this risk.(15) Our data are the first to demonstrate the value of this clinical approach, with ~~a reduced~~ lower prevalence~~risk~~ of hyponatraemia in patients practising ~~who practised~~ desmopressin escape. Patients who were instructed at initiation of desmopressin treatment, to delay or omit the dose once or more times a week had a ~~significantly~~ lower ~~risk~~ prevalence of hyponatraemia. Hyponatraemia is particularly a complication in the out-patient setting,(14) and in the absence of patient education on hyponatraemia symptoms and desmopressin

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escape, it can quickly become life-threatening. In our opinion, this method should be instructed at every initiation of desmopressin therapy, as it is an approach resulting in immediate cost-free health ~~-~~care improvements i.e., reduced ~~risk~~ prevalence of life-threatening hyponatraemia and hospitalisation~~s~~. ~~Fur~~Future~~ther~~ prospective studies should investigate whether this method indeed leads to lower risk for hyponatraemia~~hyponatraemia rates~~. Furthermore, in paediatric patients a more careful regimen is needed, and parents must be educated about hyponatraemia as a result of inappropriate management of desmopressin and fluid intake.(16)

Our data also show that a large number of patients (n=71) were unable to source desmopressin during hospitalisation when they were 'nil by mouth'/'nil per os' and without intravenous fluid replacement. Many of these patients reported ~~classic~~ symptoms of dehydration. Previously, Behan and colleagues reported concerningly high rates of hypernatraemia~~,~~ particularly~~especially~~ in in-hospital settings, most likely as a result of inappropriate management.(14) On the other hand, once admitted with hyponatraemia, physicians intuitively tend to discontinue desmopressin treatment.(17) This can lead to rapid overcorrection of serum sodium and result in severe neurological injury, if not appropriately monitored.(17) These~~is~~ findings points to the fact that the in-hospital management of patients ~~with cDI~~ should be led, or at least accompanied by, a specialist since patients with cDI are known to be highly vulnerable to rapid volume depletion in the context of severe illness if not adequately managed.(4, 18) Concern about mismanagement and delay of appropriate treatment led to a recent call for a campaign to increase awareness and education of medical personnel, and the request to include desmopressin as a high-alert medication with 24-h access in hospitals.(19) Consequently, the Society for~~of~~ Endocrinology UK published a ~~set-up a~~ clinical guidance covering the in-hospital management ~~developed by team of experts~~.(20)

Our data indicate a high prevalence of psychological co-morbidities in cDI, particularly heightened anxiety, depressed mood, sleeping difficulties, and lower sexual drives, consistent with small patient studies.(6, 21, 22) The patients also reported a reduced QoL, despite reduction of polyuria~~,~~ with desmopressin therapy. Impaired QoL and psychological changes in patients with APD are well

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recognised, and replacement therapy improves symptoms.(23, 24) In contrast, ~~only~~ few attempts have been made to evaluate psychological co-morbidities in isolated cDI. The available data suggest that reduced QoL is partly explained by fluctuations in desmopressin efficacy, leading to changes in symptom control, or by concomitant pituitary hormone deficiencies.(5, 25, 26) Our data show ~~clearly~~ that the reduction in QoL is equally apparent in isolated cDI and combined pituitary dysfunction, which challenges the assumption that concomitant pituitary hormone deficiencies are largely responsible.

Oxytocin (OT), the second neuropeptide released from the posterior pituitary, is known to mediate neuropsychiatric effects, including antidepressant, anxiolytic, and socioemotional functioning properties, suggesting a potential role for OT deficiency in the increased psychopathology ~~reported by our patients~~. This is supported by the results of a recent study.(6) ~~There has been gathering interest in the potential role of OT deficiency in a variety of neuropsychiatric and developmental disorders, and~~ ~~o~~Interestingly, one study reported that a single dose of intranasal OT improved emotion recognition in ten patients with craniopharyngioma and concomitant cDI. Conversely, in neuropsychiatric conditions intranasal OT has shown inconclusive results.(27) ~~Furthermore, OT is essential for milk ejection and appears to play a role in human sexual responses.(37) Our data show that a high proportion of female patients report difficulties in breastfeeding and low levels of sexual arousal, either of which are potentially attributable to an underlying dysfunction of the OT system; however, this remains speculative at this point. Compared to a large survey in the general population (n=1437), our data indicate higher rates of difficulties (e.g., low milk volume in 25% of patients with cDI versus 13% in the normal population).(38)~~ Future studies to investigate whether OT deficiency occurs in cDI, and whether treatment improves psychological symptoms, would be of interest.

According to National Health Service (NHS) England and the National Reporting and Learning System, 471 adverse incidents were reported from 2009 to 2015 involving desmopressin treatment.(4) Of these, prescription of the incorrect dose (*n*=56) and dose omission (*n*=76), were the most common errors. Tragically, four of these dose omissions resulted in death from severe dehydration.(4, 28) Consequently, ~~As a consequence,~~ the NHS ~~England~~ sent an alert to all doctors informing them of the risk

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of omitting this life-sustaining medication.(4) In line with this, 24% of the patients in our survey reported problems accessing desmopressin during routine or emergency hospitalisations, most commonly due to non-availability. Owing to its rarity, cDI is a neglected condition among healthcare professionals, and increased awareness of this disease is urgently needed. In addition, cDI is often confused with DM. Patients in our survey indicated high rates of confusion with DM and insufficient understanding of cDI amongst healthcare professionals; both together can significantly increase the risk of mismanagement during hospitalisation, as indicated in this survey. Future survey studies could explore the knowledge of healthcare professionals on cDI and confirm the validity of the patient's perspective. Re-naming of cDI and avoiding the word 'diabetes' could help healthcare professionals understand that cDI requires specialist life-sustaining therapy, which is distinct from DM. Several patient representative associations and foundations strongly support this approach. The majority of patients suggested 'AVP deficiency' or 'vasopressin deficiency', and of particular importance for patients was not to use 'diabetes' in the name. For the nephrogenic form, 'AVP resistance' or 'vasopressin resistance' could be suggested.(29) A working group was recently set up by the main endocrine societies worldwide to discuss and propose ~~possible~~ alternative names for cDI.

The main limitation of the study is that due to the survey design we cannot make causal inferences. ~~We W we~~ have no control group from the general population or patients with isolated APD for comparison ~~of responses.~~ ~~We have~~and no standardized longitudinal assessment of outcomes for patients with and without cDI. Since it was not our intent to assess causal effects, we did not use causal inference methods or adjust for ~~confounding~~confounding, and no weighting ~~analysis~~ was performed. While there is~~There is, however~~, substantial data showing higher psychological co-morbidities in APD compared with the background population. ~~Furthermore ,~~ psychological burden could be associated with the underlying disease. As our data indicate that lower QoL and psychological co-morbidities are comparable in patients with isolated DI and combined APD, it is reasonable to interpret our results as showing a higher psychological burden for patients with cDI than in the general population. The second main limitation is that due to the anonymous ~~web-based~~ survey design, we have no empirical information on the

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representativeness of our very large sample. Our approach allowed us to include a very large sample and we assume that it reflects the views of patients, but we cannot rule out that selection bias affected our findings; however, we used a broad recruitment strategy, through social media, online dissemination, and personal contacts, and all actively recruited patients were contacted ~~randomly~~ without any pre-specified~~ific~~ eligibility criteria. In our survey, 77% of the participants were females and the impact on psychological outcomes ~~may be assumed~~is unclear; however, sex-stratification showed no major differences in our results. Third, also due to anonymity~~ of the survey~~, response rates or differences according to each health-care system could not be analysed. Finally,~~ In addition,~~ the reliability of self-reported data, especially for unawareness of hyponatraemia not leading to hospitalisation, the difficulty in interpreting potential anterior pituitary dysfunction such as hypothyroidism and GH deficiency, and the lack of information about other co-morbidities should be considered as a limitation. However, the outcomes of our survey are significant, objective events which patients most likely remember very well, limiting the potential impact of recall bias.

In summary, our data underline the need to provide healthcare professionals with more information about cDI and its management, and to better educate patients about the strategy of desmopressin escape~~ which can reduce the risk of life-threatening hyponatraemia~~. More research is needed on the prevalence of psychological co-morbidities and possible treatment options in cDI. Furthermore, the re-naming of cDI should be actively considered by members of the international endocrinology societies.

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Contributors

CA designed the questionnaire, which was then modified and refined with input from all authors, contributed to data collection, analysis, and interpretation, did the literature search, and wrote the manuscript. MCC edited the questionnaire, contributed to data analysis and data interpretation, edited the manuscript, and supervised all steps of the conduct of the study. LGH contributed to the data interpretation and edited the manuscript. All other co-authors contributed to data collection, contributed to data interpretation, and revised the manuscript. All authors had access to all the data and had final responsibility for the decision to submit for publication.

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Declaration of interest

We declare no competing interests.

Data sharing

We may share de-identified, individual participant-level data that underlie the results reported in this Article and related documents, including the study protocol and the statistical analysis plan. Data will be available with the publication of our main manuscript on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding author. The steering committee of this study will discuss all requests and decide based on the scientific rigor of the proposal whether data sharing is appropriate. All applicants are asked to sign a data access agreement.

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FIGURE CAPTIONS

Figure 1 Aetiologies of central diabetes insipidus

Bar plots represent each aetiology category's proportion for isolated central diabetes insipidus (cDI, in blue) and patients with combined central diabetes insipidus and anterior pituitary dysfunction (cDI & APD, in red).

Figure 2 Anterior pituitary dysfunction

Bar plots representing numbers of patients with combined central diabetes insipidus and anterior pituitary dysfunction in each category grouped according to the hormones. TSH= thyroid-stimulating hormone, ACTH= adrenocorticotropic hormone, LH/FSH= luteinizing hormone/follicle-stimulating hormone.

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Figure 3 Type of desmopressin preparation

Bar plots represent the proportion of each desmopressin preparation. s.c. = subcutaneous.

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Figure 1

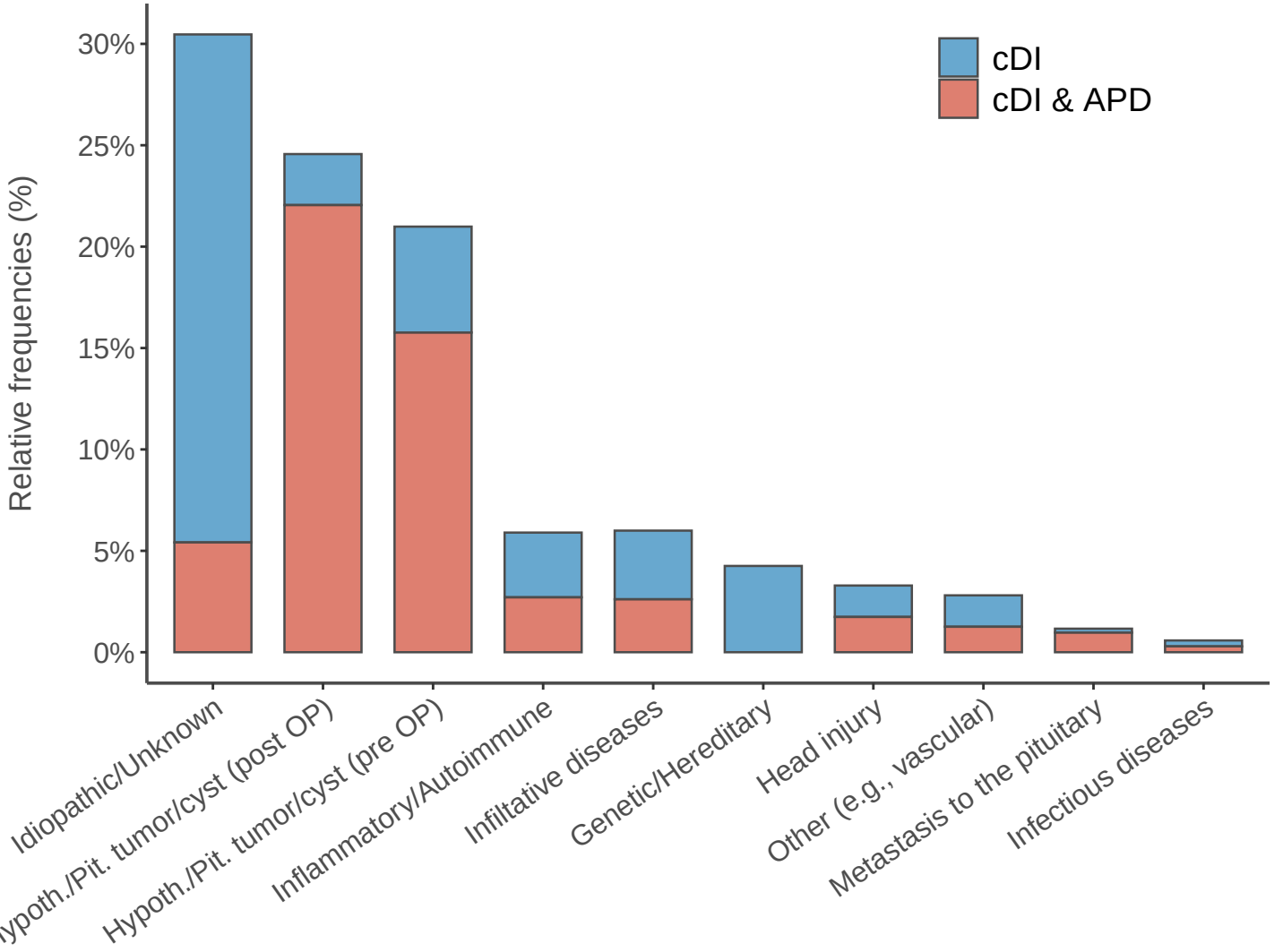

cDI
cDI & APD
Relative frequencies (%)
30%
25%
20%
15%
10%
5%
0%
Idiopathic/Unknown
Hypoth./Pit. tumor/cyst (post OP)
Hypoth./Pit. tumor/cyst (pre OP)
Inflammatory/Autoimmune
Infiltative diseases
Genetic/Hereditary
Head injury
Other (e.g., vascular)
Metastasis to the pituitary
Infectious diseases

Figure 2

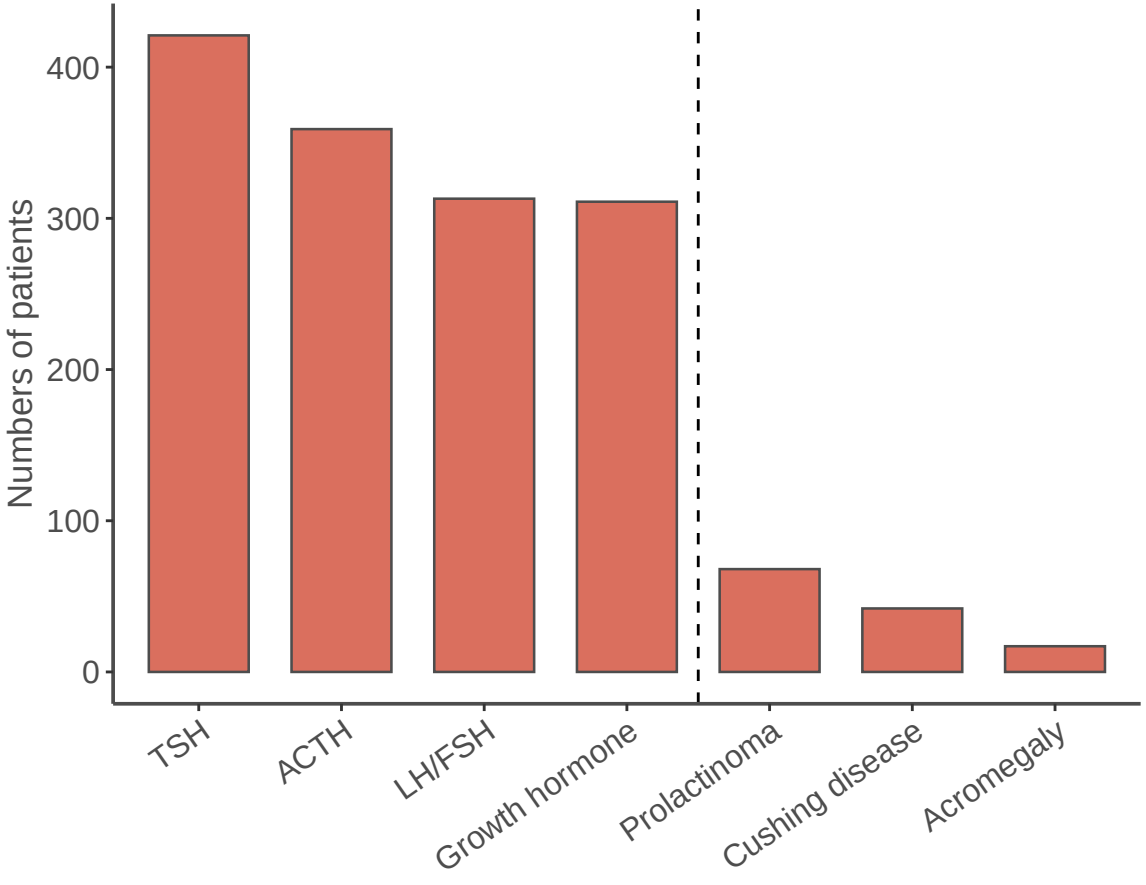
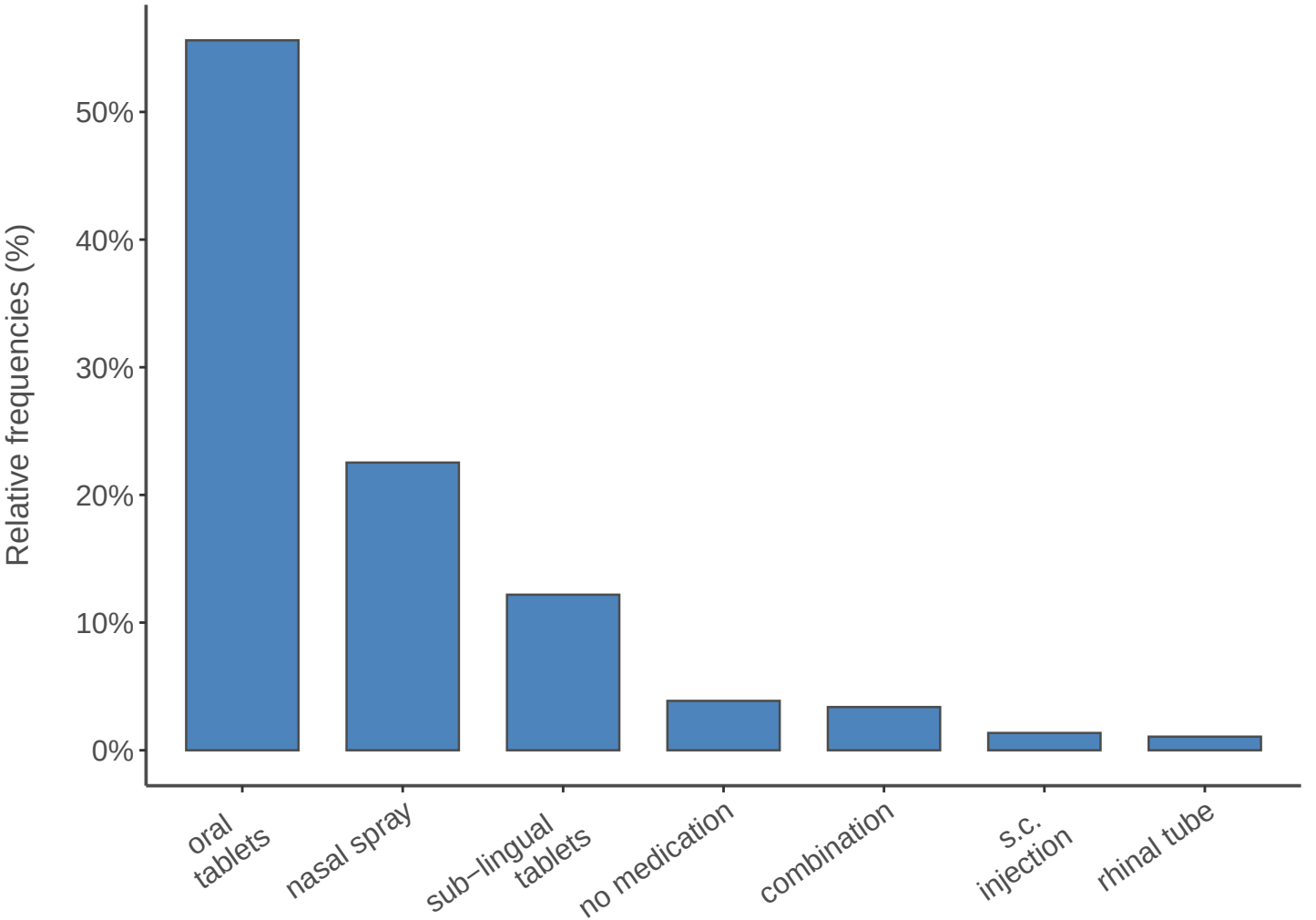

Numbers of patients
400
300
200
100
0
TSH
ACTH
LH/FSH
Growth hormone
Prolactinoma
Cushing disease
Acromegaly

Figure 3


Relative frequencies (%)
50%
40%
30%
20%
10%
0%
oral tablets
nasal spray
sub−lingual tablets
no medication
combination
s.c. injection
rhinal tube

Tables

Table 1 Baseline characteristics

	Full dataset	Isolated posterior pituitary dysfunction		Anterior and posterior pituitary dysfunction	
		adults	children/adolescent	adults	children/adolescent
n	1034	444	44	499	47
Age, years	42 [32-53]	44 [35-53]	7 [5-12]	44 [34-54]	11 [7-15]
Sex, female	794 (77)	368 (83)	20 (45)	389 (78)	17 (36)
Sex, male	240 (23)	76 (17)	24 (55)	110 (22)	30 (64)
Weight, kg	77·1 [63·0-95·0]	77·1 [65·0-93·9]	32 [20-43]	82·0 [68·0-98·0]	44·9 [35·0-61·2]
Height, cm	165 [158-173]	167 [160-173]	136 [122-155]	168 [160-174]	141 [114-157]
Body-mass index, kg/m²	27·6 [23·3-32·7]	27·4 [23·4-32·5]	16·8 [12·2-19·2]	29·1 [24·9-33·4]	21·7 [19·0-27·5]
Duration of cDI, years	9·0 [3·0-19·0]	9·0 [3·0-23·0]	3·0 [1·0-5·0]	10·0 [3·0-19·0]	4·0 [2·5-7·0]
Symptoms prior to diagnosis, years	0·3 [0·1-1·0]	0·5 [0·2-2·0]	0·2 [0·1-0·7]	0·2 [0·1-1·0]	0·1 [0·0-0·3]
Symptoms at the time of diagnosis					
Polyuria [A]	930 (90)	412 (93)	42 (95)	433 (87)	43 (91)
Polydipsia [A]	905 (88)	410 (92)	39 (89)	420 (84)	36 (77)
Nocturia [A]	810 (78)	386 (87)	35 (80)	365 (73)	24 (51)
Aetiologies of central diabetes insipidus					
Idiopathic/unknown	315 (30)	240 (54)	19 (43)	51 (10)	5 (11)
Hypothalamic/ Pituitary tumour/cyst (post-surgery)	254 (25)	26 (6)	0 (0)	211 (42)	17 (36)
Hypothalamic/ Pituitary tumour/cyst (pre-surgery)	217 (21)	48 (11)	6 (14)	157 (31)	6 (13)
Infiltrative disease (e.g., sarcoidosis, Langerhans cell histiocytosis)	62 (6)	25 (6)	10 (23)	16 (3)	11 (23)
Inflammatory/autoimmune (e.g., hypophysitis)	61 (6)	30 (7)	3 (7)	28 (6)	0 (0)
Genetic/familial	44 (4)	40 (9)	4 (9)	0 (0)	0 (0)
Head injury	34 (3)	16 (3)	0 (0)	17 (3)	1 (2)
Other causes (e.g., vascular, congenital)	29 (3)	15 (3)	1 (2)	7 (1)	6 (13)
Metastasis to the pituitary (e.g., lymphoma, breast cancer, lung cancer)	12 (1)	1 (0)	1 (2)	10 (2)	0 (0)
Infectious diseases (e.g., meningitis, encephalitis, tuberculosis)	6 (1)	3 (1)	0 (0)	2 (0)*	1 (2)

Data are presented in median [IQR] and numbers (%) for the full dataset, patients with isolated posterior pituitary dysfunction, and patients with combined anterior/posterior pituitary dysfunction. n=numbers, A= remaining patients could not recall the symptoms (e.g., diagnosed in childhood). *This column will not add up to 100% because of rounding.

Table 2 Psychological co-morbidities

	Full dataset (n=1034)	Isolated posterior pituitary dysfunction (n=488)	Anterior and posterior pituitary dysfunction (n=546)
Psychological problems or changes since diagnosis	369 (36; [33-39])	173 (35; [31-40])	196 (36; [32-40])
heightened anxiety	258 (25; [22-28])	115 (24; [20-27])	143 (26; [23-30])
sleep disturbance	263 (25; [23-28])	113 (23; [19-27])	150 (27; [24-31])
depressed mood	239 (23; [21-26])	99 (20; [17-24])	140 (26; [22-29])
stress management disturbance	181 (18; [15-20])	86 (18; [14-21])	95 (17; [14-21])
change in eating habits	168 (16; [14-18])	82 (17; [13-20])	86 (16; [13-19])
change in personality	124 (12; [10-14])	51 (10; [8-13])	73 (13; [11-16])
Documented psychological condition after the diagnosis	111 (11; [9-13])	41 (8; [6-11])	70 (13; [10-16])
Reduced *QoL* after the diagnosis	660 (64; [61-67])	308 (63; [59-67])	352 (64; [60-68])
social activities	538 (52; [49-55])	249 (51; [47-55])	289 (53; [49-57])
recreation and fun	493 (48; [44-51])	234 (48; [44-52])	259 (47; [43-52])
physical wellbeing	476 (46; [43-49])	218 (45; [40-49])	258 (47; [43-51])
mental wellbeing	414 (40; [37-43])	192 (39; [35-44])	222 (41; [37-45])
Subjective rates on a VAS, median [IQR]			
QoL*, B	6 [4-7]	6 [4-8]	6 [4-7]
Ability to trust*, B	7 [4-8]	7 [4-8]	7 [4-8]
Social interaction*, B	7 [5-8]	7 [6-8]	7 [4-8]
Sexual arousal*, A, B	3 [2-7]	4 [2-8]	3 [1-6]
Anxiety level in general life*, C	6 [3-8]	6 [3-8]	6 [3-7]

Data presented in median [IQR] and n (%; [95%-CI]).*Rated on a visual analogue scale (VAS) from 0 (=minimum/no) to 10 (=maximum/extreme). A = answered by 819 patients. B = low score on this parameter reflects more adversely affected. C = high score on this parameter reflects more adversely affected. n= numbers. QoL= quality of life

EKNZ

Ethikkommission
Nordwest- und
Zentralschweiz

Präsident
Prof. Christoph Beglinger
Vizepräsidenten
Dr. Angela Frotzler
Dr. Marco Schärer

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4031 Basel

Basel, 31. Januar 2022 / SK

Clarification of responsibility of the Ethics Committee Northwest and Central Switzerland (EKNZ)

Project-ID	Req-2021-00611
Project title	Assessment of the characteristics of patients with diabetes insipidus (DI) – from diagnosis the management of the condition – the DImond survey
Submission Date	31.05.2021
Applicant	Dr. Cihan Atila

Decision

The research project does not fall under the scope of the Human Research Act, because your project please select an option. An authorisation from the ethics committee is therefore not required and the EKNZ is not responsible for its review.

Fees

Tariff code: 6.0 **Amount:** **CHF 200.-**
In accordance with the current swissethics fee schedule.

Yours sincerely,

i.V.

Prof. Christoph Beglinger
President of the Ethics Committee
Northwest and Central Switzerland / EKNZ

STROBE Statement

	Item	Recommendation	Reported on manuscript page
Title and abstract			
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	a) 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	b) 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(a) *Cohort study*—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—give the eligibility criteria, and the sources and methods of selection of participants	web-based survey a)8/9 (and supplementary p2)
		(b) *Cohort study*—for matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—for matched studies, give matching criteria and the number of controls per case	b) NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9 (objectives and outcomes)
Data sources/ measurement	8*	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Supplementary p14 (see CRF with all questions)
Bias	9	Describe any efforts to address potential sources of bias	Supplementary p3 & 5
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	a)9/10
		(b) Describe any methods used to examine subgroups and interactions	b)NA
		(c) Explain how missing data were addressed	c)supplementary p4
		(d) *Cohort study*—if applicable, explain how loss to follow-up was addressed *Case-control study*—if applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—if applicable, describe analytical methods taking account of sampling strategy	d)NA
		(e) Describe any sensitivity analyses	e)NA
Results			
Participants	13*	(a) Report the numbers of individuals at each stage of the study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	a)11
		(b) Give reasons for non-participation at each stage	b)supplementary p4 (only complete surveys were saved / analysed)
		(c) Consider use of a flow diagram	c)NA (only complete surveys were saved / analysed)
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders	a) 11 and Table 1
		(b) Indicate the number of participants with missing data for each variable of interest	b) NA (no missing data were generated, supplementary p4)
		(c) *Cohort study*—summarise follow-up time (eg, average and total amount)	c)NA (web-based survey without follow-up)
Outcome data	15*	*Cohort study*—report numbers of outcome events or summary measures over time *Case-control study*—report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—report numbers of outcome events or summary measures	12-16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	a) 12-16
		(b) Report category boundaries when continuous variables were categorised	b) 12-16
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	c) NA
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses	Supplementary p7
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give such information separately for cases and controls in case-control studies, and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the websites of *PLoS Medicine*, *Annals of Internal Medicine*, and *Epidemiology*). Separate versions of the checklist for cohort, case-control, and cross-sectional studies are available on the STROBE website.

Table: **The STROBE statement—checklist of items that should be addressed in reports of observational studies**

STROBE Statement
Strengthening the reporting of observational studies in epidemiology

STROBE Statement—Items to be included when reporting observational studies in a conference abstract

Item	Recommendation	
Title	Indicate the study's design with a commonly used term in the title (e.g cohort, case-control, cross sectional)	checked and applied
Authors	Contact details for the corresponding author	checked and applied
Study design	Description of the study design (e.g cohort, case-control, cross sectional)	checked and applied
Objective	Specific objectives or hypothesis	checked and applied
Methods		
Setting	Description of setting, follow-up dates or dates at which the outcome events occurred or at which the outcomes were present, as well as any points or ranges on other time scales for the outcomes (e.g., prevalence at age 18, 1998-2007).	Stated as web-based survey
Participants	*Cohort study*—Give the most important eligibility criteria, and the most important sources and methods of selection of participants. Describe briefly the methods of follow-up *Case-control study*—Give the major eligibility criteria, and the major sources and methods of case ascertainment and control selection *Cross-sectional study*—Give the eligibility criteria, and the major sources and methods of selection of participants	web-based survey - total number of patients is given
	Cohort study—For matched studies, give matching and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	Clearly define primary outcome for this report.	due to explanatory design - no primary but several outcomes
Statistical methods	Describe statistical methods, including those used to control for confounding	NA
Results		
Participants	Report Number of participants at the beginning and end of the study	checked and applied
Main results	Report estimates of associations. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Report appropriate measures of variability and uncertainty (e.g., odds ratios with confidence intervals	checked and applied
Conclusions	General interpretation of study results	checked and applied