Author's response to reviews

Title: Sudden cardiac death in the young (5-39 years) in the canton of Vaud, Switzerland

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Cover Letter

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Type of the article: Research article
Authors: Fanny Hofer; Florence Fellmann; Jürg Schläpfer; Katarzyna Michaud

All of the corrections have been highlighted with yellow font colour in the manuscript.

Referee 1:

Major issues:
The incidence of SCD, in my opinion, must rely on somewhat reliable data. I can’t see that every death has been investigated in relations to circumstances relating to the death. Hence, no information indicating that the death was sudden and unexpected exists.

We completely agree that the determination of the incidence of SCD must be based on reliable data. We acknowledge that we do not have any definitive information indicating that the death was sudden and unexpected. At present we are unable to obtain more information from the Swiss death certificates as they are much more succinct than those administered in Denmark, for example as we mentioned in our manuscript (L193). We added the reference of recommendations concerning the medical attestations of the causes of death (http://www.iump.ch/Publications/pub/DirCauseDeces_1991.pdf). On page 53 of this document there is a form provided for statistical purposes, to be filled out by the practitioner who certifies the death. We also detailed the procedure of data transmission, including that of the autopsy results in the manuscript:

“In the canton of Vaud, the general practitioner who completes a death certificate has to determine if the death was natural, violent or undetermined. If the death is determined to be violent or undetermined, a medico-legal investigation is usually undertaken but does not systematically include an autopsy. A forensic autopsy is performed if the appropriate authorities deem it necessary. Familial consent is not required for a forensic autopsy. If the death is determined to be due to natural causes, a clinical autopsy can be performed with the consent of the living relatives. Several weeks after the death, the general practitioner who signed the death certificate is contacted by the Swiss Statistics Office and is asked to complete the medical attestation (page 53 of these recommendations) concerning the cause of death and any existing concomitant diseases [25]. Among others, the following questions are asked: 1) Was an autopsy performed? 2) If so, are the results available? and 3) If performed, did the autopsy confirm the previously determined cause of death? The general practitioner who signs the death certificate is not, however automatically informed if an autopsy was performed or not, especially in the forensic context. He or she rarely has access to forensic autopsy results, as they are usually transmitted only to juridical authorities. This being the case, the forensic pathologist who
performed the autopsy is not automatically questioned about the results of the post-mortem investigations. At present the autopsy results are not required for statistical purposes, however, their integration into the statistical analyses is strongly encouraged as noted in the recommendations mentioned above, “if possible, the results of autopsy should be awaited before validation of the cause of death”.

1122 deaths all together are not that many. Why did you focus on selected deaths? Could you retrieve more information on each case, e.g. prior disease, medication, family history, circumstances relating to the death, to further elucidate with death were sudden and unexpected? To me, this approach would be more informative.

As stated in the methods, this study was based on available anonymous registries and we did not have access to individual medical records. It was, therefore, not possible to obtain more information from the death certificates alone.

As you correctly state, cause of death registries often fail to be accurate. To me, the proxy (cardiovascular death equals SCD) is unusable. If you do not have access to the information above, I think you need to modify your results. As such, I wouldn’t call these deaths SCD, but merely cardiovascular deaths. And then discuss from thereon.

We agree with the reviewer that the term “SCD” is not ideal given the context of this study. Nevertheless, we think that categorizing these deaths as cardiovascular is also questionable and too vague. We have chosen, therefore, to change the term “SCD” to “presumed SCD”, and we added a sentence in the “Limitations” section: “The available anonymous data does not allow for the distinction between SCD and other cardiovascular deaths. For this reason the term “presumed SCD” has been chosen. Similar limitations have been reported in other published studies of this nature [9, 32, 33].”

We would like to emphasize that this limiting factor is inherent to this type of retrospective study, and was previously acknowledged in other similar studies as written in our manuscript (L219-20) “Our study confirms that the use of death certificates in the statistical analysis of the causes of mortality is far from ideal as was already suggested by other authors [9, 32, 33].”). Improvements in both the death certificate form and in the formation of medical students, as well as the development of a structured registry of SCD could ameliorate the data quality in the future. Nevertheless, preliminary studies are the first step to generate debate on these issues.

2) Incidence rates: These figures include non-autopsied cases. From prior studies, it is well known that only approximately half of possible SCD (SD) is in fact SCD after autopsy. In addition, as already mentioned you do not know if all deaths were sudden and unexpected. Hence, these incidence rates must be taken with great caution. In relations to above concern, I think you should reconsider using the term SCD in conjunction with the incidence rates you present…

We agree with the reviewer. Again, our study is based on available anonymous statistical data which include autopsied and non-autopsied cases. On the basis on this data, it is impossible to distinguish between SD and SCD with certitude. Considering the remark, we have modified the
term “incidence of SCD” which now reads “incidence of presumed SCD”.

As aforementioned, we added a sentence in the “Limitations” section: “The available anonymous data does not allow for the distinction between SCD and other cardiovascular deaths. For this reason the term “presumed SCD” has been chosen. Similar limitations have been reported in other published studies of this nature [9, 32, 33].” We would like to point out that our results are in accordance with other studies published in the literature (Table 4).

**Minor issues:**

Page 6. Sentence starting with “An autopsy was performed....” This sentence is unclear, perhaps because the numbers are incorrect? (121 vs 124). Please rephrase in appropriate.

As mentioned in our manuscript, we had two principle data sources: SCRIS and IUMSP. SCRIS provided general demographic statistical data on the total population, broken down by age group and cause of death. IUMSP provided information on the autopsies performed.

We modified our manuscript as follows (L134-9): “The cause of death remained undetermined or unclear for 121 deaths that could possibly have been SCD (data received from SCRIS). These cases were more frequent in the 30 to 39 year age category (74/121; 61%) (Table 2). According to data received from IUMSP, an autopsy was performed in 13.7 % of cases in this category of deaths and the autopsy results enabled the confirmation only for 2 deaths registered in the statistical data (Table 3). It was unknown if an autopsy was performed or not in 94 cases (75.8%) (Fig.2).”

Page 7. Line 3-5. What was the confirmation of the autopsies? Cause of death? Sudden and unexpected death? Please clarify.

We were not able to obtain more details based on the anonymity of the data, as previously explained. The deaths were categorized as transport accidents in the official statistical data. In this category, traumatic lesions were probably observed that could explain the death, but the system does not allow for verification of whether or not the victim was driving the car, and if a sudden collapse (for example related to coronary thrombosis) could be the origin of the fatal event, this especially if an autopsy was not performed. We were also unable to determine if the results of an eventual autopsy were available to the service codifying the cause of death for statistical purposes.

The autopsy results are not systematically required for statistical purposes. It is, however, stated in the recommendations concerning the medical attestation (page 6 [http://www.iумsp.ch/Publications/pub/DirCauseDeces_1991.pdf](http://www.iумsp.ch/Publications/pub/DirCauseDeces_1991.pdf)), “if possible, the results of autopsy should be awaited before validation of the cause of death”.

We have stated in the manuscript that “it was impossible to determine if the cause of death was modified according to the post-mortem examination in the official published statistics” (previous version line 169, new version line 206).
Table 1: Were there no deaths under age 15?

There were no deaths under the age of 15 in this category. We modified the legend of table 1.

Table 3: Do I understand it correct, that only 4/11 drownings actually were drownings? What was then the cause of death?

Yes, you understood correctly. According to the available statistical data, for 4 of the 11 drownings the cause of death was confirmed by autopsy. Autopsy information was not available for the remaining 7 cases. As aforementioned, we were not able to find more precise information due to the anonymity of the data. This aspect was addressed in the “Limitations” section.

Table 3: The percentage of "no data concerning autopsy" are very high in ill-defined causes. Do you have an explanation?

We were also very surprised to find such a high percentage, especially in the category of “ill-defined and unknown causes” as noted in the “Discussion” section. This problem is likely related to contents of the medical certificate regarding the cause of death and to the fact that the information concerning the autopsy is not systematically available to the first practitioner who completes this document. More information could be obtained from an autopsy but we were unable to determine if an autopsy was performed or not. If performed, we were unaware if the results were requested from the pathologist, or if the results modified the codified cause of death. As expressed in our manuscript: “it was impossible to determine if the cause of death was modified according to the post-mortem examination in the official published statistics.”

Table 4: Winkel et al (ref 5) is nationwide including all deaths (hence general population, both autopsied and non-autopsied)

The correction was made in the table.

Referee 2:

Major Compulsory Revisions

1. Information on whether or not autopsy was performed and the results of autopsy are missing in a significant number of cases. What are the reasons for this missing data? And does the IUMSP also provide the result of the autopsy performed or did the authors use other methods to obtain these results?

We deem it necessary to explain in more detail the system of transmission of the autopsy results and codification of the cause of death. We propose the addition of the following explanation to the manuscript (as already mentioned to referee 1):
“In the canton of Vaud, the general practitioner who completes a death certificate has to determine if the death was natural, violent or undetermined. If the death is determined to be violent or undetermined, a medico-legal investigation is usually undertaken but does not systematically include an autopsy. A forensic autopsy is performed if the appropriate authorities deem it necessary. Familial consent is not required for a forensic autopsy. If the death is determined to be due to natural causes, a clinical autopsy can be performed with the consent of the living relatives. Several weeks after the death, the general practitioner who signed the death certificate is contacted by the Swiss Statistics Office and is asked to complete the medical attestation (page 53 of these recommendations) concerning the cause of death and any existing concomitant diseases [25]. Among others, the following questions are asked: 1) Was an autopsy performed? 2) If so, are the results available? and 3) If performed, did the autopsy confirm the previously determined cause of death? The general practitioner who signs the death certificate is not, however automatically informed if an autopsy was performed or not, especially in the forensic context. He or she rarely has access to forensic autopsy results, as they are usually transmitted only to juridical authorities. This being the case, the forensic pathologist who performed the autopsy is not automatically questioned about the results of the post-mortem investigations. At present the autopsy results are not required for statistical purposes, however, their integration into the statistical analyses is strongly encouraged as noted in the recommendations mentioned above, “if possible, the results of autopsy should be awaited before validation of the cause of death”.

We had stated in our paper that “it was impossible to determine if the cause of death was modified according to the post-mortem examination in the official published statistics” (L206-8)

Information on whether or not autopsy was performed and the results of autopsy are missing in a significant number of cases. What are the reasons for this missing data?

In our opinion and considering all legal aspects, this is related to the fact that the transmission of the autopsy results is not obligatory to determine the cause of death for statistical purposes.

And does the IUMSP also provide the result of the autopsy performed or did the authors use other methods to obtain these results?

IUMSP does not provide the results of the autopsies performed. The results of an eventual autopsy are transmitted (not automatically) in anonymous form to the Swiss Statistics Office in order to codify the cause of death, but only if the (forensic) pathologist is contacted. IUMSP transmits the anonymous information concerning the number of autopsies, but not the results.

Minor essential revisions:
1. P4 150: “The Canton of Vaud is …”. These two sentences should be moved to the methods section.

The correction has been made.
2. P7 l113: “The average population of individuals who were between 5 and 39 years of age between 2000 and 2007 was of 292’546 inhabitants.” This sentence should also be moved to the methods section.

The correction has been made.

3. Despite the table legend, Table 3 is difficult to understand. Perhaps it is better to change this table into a flowchart. And the denominator in the percentages of cases in which cause of death was confirmed after an autopsy should be the total number in which autopsy was performed, not the total number of cases.

We recalculated the percentage of cases where an autopsy confirmed the case of death against the total number of autopsies performed and modified Table 3 accordingly. We considered making a flowchart, but estimated that some data would be lost as compared to the table.

Discretionary Revisions

1. P4 l38: “… and often occur in otherwise healthy individuals.” In our experience most sudden death events in the young occur in individuals with a relevant medical history. Please note that in most studies on the epidemiology of sudden (cardiac) death in the young, individuals with a relevant medical history are excluded.

We modified the sentence as follows. “About half of the cardiac deaths in young individuals are sudden, and often occur in individuals considered to be in good health”.

2. P4 l42: “… but only by performing postmortem genetic analyses.” Another strategy, which is probably applied more often, is to screen the first-degree relatives for inherited cardiac diseases (Heart Rhythm 2010;7:1383-9; Eur Heart J 2008;29:1670–80).

We modified the sentence according to the suggestions: “Most of these disorders cannot be detected through a regular autopsy, but only by performing post-mortem genetic analyses, a.k.a. molecular autopsies or screening the first-degree relatives for inherited cardiovascular diseases”.

We added the suggested references.

3. Are there any circumstances in which autopsy is mandatory by law in Switzerland? And what kind of physicians are involved in cases of sudden death in the young and what is their role in requesting an autopsy? It would be interesting to get more information on the reasons for the low autopsy rate.

We explained the current autopsy practice in our answer to the first remark. We think that the reasons underlying the low autopsy rate are quite complex (financial, legal, religious etc).

Editor requests

Data

We completed the “Data” section as follows:
This retrospective study relied on the gathering of statistical data from both the Cantonal Statistical Research and Information Service (SCRIS) and the University Institute of Social and Preventive Medicine (IUMSP) in the canton of Vaud, Switzerland from 2000 to 2007. The SCRIS provided general demographic statistical data on the total population, broken down into age groups and the cause of death. SCRIS was contacted by indicated Email address info.stat@vd.ch on the website www.scris.vd.ch/mortalité. The IUMSP provided the information regarding the autopsies performed and was contacted by the website http://www.iumsp.ch. The general statistical information was obtained from the website of Swiss Statistics http://www.statistique.admin.ch contacted by gesundheit@bfs.admin.ch and info.dem@bfs.admin.ch

**Ethical aspects:**

We modified the manuscript as follows:

“The protocol of this study was evaluated by the regional ethical committee for research. No consent was requested as study was performed retrospectively on anonymous data, which was in accordance with the existing law”.

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