Author’s response to reviews

Title: Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis

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Version: 1 Date: 22 Oct 2015

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Response to Reviewers

Manuscript:

BCAN-D-15-00259 (“Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis”)

Authors:

Jason Gurney, Caroline Shaw, James Stanley, Virginia Signal, Diana Sarfati

Reviewer 1:

The reviewed manuscript provides a systematic review and meta-analysis of 3 case-control studies that evaluated marijuana use and risk of testicular germ cell tumors (TGCT). Overall the authors present a thorough review of the literature that expands upon the previous meta-analysis of the 3 published studies that summarized results based on overall TGCT but not by histologic subtype.

Thank you for this comment.

Major comments:

The authors state that odds ratios and 95% confidence intervals were abstracted from the manuscripts, however the results reported in both Trabert et al, and Daling et al, were provided
with only two significant digits, and the results reported in the current manuscript are based on three significant digits. The authors need to state any additional estimation that may have been used to ascertain the estimates used in the meta-analysis, as there are some inconsistencies in the data with respect to rounding.

Thank you for this important comment. The reviewer helpfully identified an error in the presentation of the results of our meta-analysis – in the original version of the manuscript, we had used the odds ratios and confidence intervals (from the source papers) to determine log-odds ratios and the corresponding standard error. The confidence intervals presented in our paper were calculated using these log-odds and standard errors, and thus the odds ratios we presented differed marginally to those presented in the original manuscripts (due to the back-transformation and rounding). We have corrected this in the revised version of our Figures and the corresponding text.

Page 9 line 2, the statement about studies matching on history of cryptorchidism is incorrect, studies adjusted for history of cryptorchidism, they did not match on this criteria.

Thank you – we have corrected the relevant section of text in the Results section, which now reads:

• “In order to maximise the comparability of cases and controls, each of the studies matched controls to cases – or adjusted in their regression modelling – for what could be considered the two strongest confounding variables (age and history of cryptorchidism).”

Page 12 lines 1-4, [26] incorrect citation, the statement regarding predisposition to current marijuana use if exposed prenatally or during early childhood isn't supported by the current citation. Further, this statement without an appropriate citation is speculative.

Thank you – this paragraph is indeed speculative, since insufficient work has been done to investigate this association. The citation has been removed, and the relevant text edited to the following:

• “In other words, it is possible that primary cannabis use could be a proxy for second-hand exposure to cannabis during the prenatal and/or early childhood period. Such exposure would be congruent with a pre-adulthood disruption to the hypothalamic-pituitary-testicular axis, albeit via a secondary rather than primary source. However this association remains speculative and further research is required regarding the role of non-primary exposure to cannabis during the prenatal and early childhood period as a risk factor for the development of TGCT.”

Given the case-control design of the summarized studies and average 10 year difference in age at interview of seminoma and nonseminoma cases, it is possible/plausible, that there is a consistent association between nonseminoma TGCT and marijuana use, because younger men were more willing to report marijuana use. This warrants further discussion by the authors.
Thank you for raising this point. We agree, and have added the following paragraph to the relevant section of the Discussion:

- “…This may suggest that any carcinogenic disruption of interest to the hypothalamic-pituitary-testicular axis occurs during (or before) puberty;[24] however it is also possible that early initiation of cannabis exposure is a marker of other mediating factors, such as duration and frequency of cannabis use later in life. Another possibility is that since those cases that developed non-seminoma tumours were younger at the time of data collection than those who developed seminoma tumours, they may have been more likely to either recall or report marijuana use. Such a scenario would have the effect of exaggerating the association between cannabis use and non-seminoma development. However, it should be noted that this exaggeration would only occur if the age-matched controls who participated in these studies were not affected by this pattern of differential reporting by age – in other words, if the cannabis use reported by controls was accurate.”

Minor comments:

Biggs et al. 2012 (PMID 18708392) provides details of control participation for the Daling et al. study.

Thank you – we have updated the relevant section of Additional File 2 with the following text:

- “8. Information on control participation is available in a separate manuscript that uses data from the same case-control study (Biggs et al., 2008).”

The sections on 'summary of meta-data for studies' and 'assessment of study quality' are redundant, the authors should consider reducing the repetitive details reported in 'summary of meta-data' section.

Thank you for this comment – we agree that the information regarding age of participants were repeated in both the ‘Meta data for included studies’ and ‘Assessment of study quality’, and have deleted this paragraph to avoid repetition.

Reviewer #2:

Page 2, lines 22-24: The part of this sentence that refers to the "three published studies" should be deleted since it is already clear from the "Methods" section of the abstract that the meta-analysis is based on three studies.

This part of the sentence has been removed.

Page 2, lines 27-31: This sentence has multiple problems. First, it is not clear what the authors mean by "focus on measurement of cannabis exposure." They should revise the sentence to be more precise. Second, the recommendation to investigate the "likely timing of meaningful cannabis exposure" is also vague, particularly given that the extant studies showed evidence that
the increased risk was among current users. Finally, by referring to the possibility that important exposure might happen in the prenatal period or in early childhood implies that exposure is occurring secondarily through smoking/consumption by the mother or other adults in the household. This should be clarified in a revised sentence to help the reader.

Thank you for these comments. We agree that this concluding statement is vague and unnecessary, and as such have removed it from the abstract.

Page 3, line 12: "prevalence rates" is an incorrect term because measures of prevalence and measures of rates are two different entities. What is described in this sentence appears to be proportions of the population that consume cannabis, so the proper term is most likely "prevalence."

Thank you for noticing this oversight. We have corrected the relevant section of text accordingly.

Page 3, line 28: The wording of this sentence gives more weight to the results of these studies than is probably justified. Please revise to say "...at least three case-control studies reported associations between..."

We have revised the relevant section of text to read:

- “In recent years, at least three case-control studies reported associations between cannabis exposure and testicular germ cell tumour (TGCT) development.[7-9]”

Page 3, line 31: The authors need to provide a citation for this "recent meta-analysis" somewhere in this sentence.

We have added the relevant citation (Huang et al., 2015).

Page 7, line 34: It is not clear what the authors mean by "consistent." Does it just mean that all three studies used age matching, or that the age matching was done in the same way in all three studies? The latter seems unlikely, since the authors later say that one study used individual matching and the other two studies used frequency matching. The authors should avoid using general words and instead convey precise information.

Thank you for this comment. We have expanded the relevant text to read:

- “Controls were either randomly derived from the community [9, 8] or the friend of cases.[7] All three studies matched on age, while two of the three studies matched on region of residence.[9, 8] Two of the three studies also matched cases and controls on race and/or ethnicity.[8, 7] Two of the three studies [9, 7] frequency-matched controls to cases, while one study individually-matched controls to cases.[8]”

Page 7, lines 45-47: It is not clear how the authors can first say that the participants in all three studies were 18-50 years of age, and then say one of the studies only included persons 18-35 years of age. It is also not correct that all three studies included 18-50 year olds, since one study
(Daling et al.) restricted its study population to men diagnosed at ages 18-44 years of age. Note also that this statement contradicts what the authors have written on the subsequent page.

Thank you for this comment. As discussed previously with respect to a comment from Reviewer One, we have removed this section of text (and the details are covered in another section).

Page 8, lines 25-27: It is not clear how the authors arrived at this conclusion based on the information presented in the published papers. In Daling et al., for example, the Methods section does not mention anything about "independent validation." And in Lacson et al., it is not clear that there was any independent review was performed, just that histologic type was coded based on the original pathology reports (a step that is normally done by the cancer registry from which the cases were identified for the study).

Thank you for this comment. As stated in the text, “Case definition was adequate for all included studies, with registry records independently validated via review of pathology records.” As the reviewer will recall, the current systematic review and meta-analysis measured study quality against the Newcastle-Ottawa Scale (NOS). (Wells et al, 2004) According to this scale, the three options available to a reviewer in terms of defining whether case definition was adequate are as follows:

1. Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records);

2. Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record;

3. No description.

We measured each study against the Newcastle-Ottawa Scale criteria using this information, and subsequently categorised each study as ‘1’ – i.e. adequate case definition with independent validation (as each study derived cases from either a cancer registry, a local cancer centre’s patient register, or a County surveillance programme). Details are summarised in the following paragraph.

Daling et al. derived cases in the first instance from a cancer registry (CSS). They then contacted each patient’s follow-up physician, and asked them if there was any reason why the man should not be included in the study. In the absence of any such reason, an introductory letter and invitation to participate was sent to the patient. In the case of Trabert et al., cases were derived in the first instance from a local cancer centre’s patient registry (from The University of Texas M. D. Anderson Cancer Center). Pathology reports for each case were then reviewed, and cases grouped according to tumour histology. In the case of Lacson et al., cases were derived in the first instance from a cancer registry (the Los Angeles County Cancer Surveillance Program). The pathology reports for each case were then reviewed, and cases grouped according to tumour histology.

Page 8, line 30: None of the studies involved a cohort. Please revise.
We have revised the text accordingly:

- “In terms of case representativeness, two of the included studies restricted their participants to those aged between 18 and 44-50”

Page 9, lines 2-3: The authors are incorrect in asserting that these studies matched controls to cases on history of cryptorchidism. This would be almost impossible to do given how infrequent this characteristic is in the general population of men.

In line with a similar comment from Reviewer One, we have corrected the relevant section of text.

Page 9, line 8: The authors should refer to these as "response proportions" since they are not "rates" in the way that this term is normally interpreted in epidemiologic research.

Thank you for the comment – however we do not agree that this is appropriate. The term ‘response rate’ is the standard terminology used for the proportion of invited participants who respond to a study (even in epidemiological settings where rates and proportions are treated differently: for example, the term is used in Rothman, Greenland, and Lash’s “Modern Epidemiology”, a leading textbook in the field).

Page 10, line 29: Sometimes the authors use the abbreviation "TC" and sometimes they use the abbreviation "TGCT". They should be consistent. Since virtually all TC are TGCT, and if in the three studies included in this meta-analysis the authors limited their case eligibility to TGCT, then that term should be used.

Thank you for noticing this oversight. The abbreviation ‘TC’ has been removed from the manuscript and replaced with TGCT.

Page 11, lines 1-2: The authors should follow this sentence with a few well-considered remarks about the evidence that dysregulation of testicular function is relevant to TGCT etiology. Certainly the evidence that aberration in testosterone itself (specifically, low testosterone) is a risk factor is fairly weak.

Thank you for this comment. We have clarified/amended the relevant section of text as follows:

- “The biological plausibility of the link between cannabis exposure and testicular cancer is thought to be related to disruptions to the hypothalamic–pituitary–testicular axis – an endocrine feedback system which, among other actions, assists with spermatogenesis.[24] It is thought that cannabis exposure – and subsequent stimulation of cannabinoid receptors – disrupts normal hormone regulation and testicular function, and that this disruption leads to carcinogenesis.[24] However, evidence regarding the association between regulation of normal testicular function and tumour development remains inconclusive; and given the complex influence of cannabinoid receptor stimulation on
multiple biological processes,[9] the path from cannabis exposure to testicular carcinogenesis remains unclear.”

Further, the authors must also acknowledge what is known about the effects of THC (or other cannabanoids) and/or signaling through cannabanoid receptors on other types of cancer. For example, there is a strong series of studies showing anti-tumor effects in colon cancer models. Thus, overall, it is not at all clear that cannabis use should have net carcinogenic effects in any particular tissue.

Thank you for this observation. While we agree with the reviewer that cannabis has shown anti-tumourogenic effects in other cancer contexts, we believe that it is outside the scope of the current review to discuss these. We also note that our revised version of the relevant text (see above) makes no general statement about the carcinogenic influence of cannabis exposure, but rather is testicular cancer-specific.

Page 11, lines 15-16: I don't think that this argument makes sense, at least as articulated by the authors. If cannabis is as likely to cause seminomas and non-seminomas, there is no reason why the age at diagnosis per se should matter in a study (whether due to the indolence of one type or some other reason) in which the age distribution of the cases is wide enough to include the ages at which both diseases typically occur. A better explanation might be differences in statistical power to detect associations for each TGCT type. Specifically, if "current" (i.e., close to diagnosis) cannabis use is the important exposure, then a larger proportion of younger (more at risk for non-seminomas) as opposed to older men (more at risk for seminomas) will be exposed, which generally leads to more statistical power. Even so, because there is considerable overlap in the age distributions for non-seminoma and seminoma, even the "difference in statistical power" explanation seems unlikely to be the reason for the difference in the associations (if seminomas were truly caused by cannabis). Finally, if the authors truly wish to ruminate in this manuscript on the possible reasons for an association with non-seminomas but not seminomas, then they probably should spend some time reviewing the literature that discusses the molecular and pathophysiologic bases for these two histologic types.

Thank you for this comment. We largely agree with the reviewer’s assessment. We have removed the paragraph in question (which included the statement regarding the potential indolence of non-seminoma tumours), and instead have re-framed the subsequent section regarding the potential explanations for why non-seminoma tumours are associated with TGCT development, but not seminoma tumours. The relevant text now reads:

• “The observation of an association between cannabis use and non-seminoma TGCT development – but not seminoma development – is intriguing. As discussed by Skeldon and Goldenberg,[25] this association directs our attention to puberty (rather than later in life) as the key point of exposure. Non-seminoma tumours are typically diagnosed seven [12] to ten [13] years earlier than seminoma tumours. Interestingly, one study included in the current review that asked cases and controls about the timing of their first cannabis use showed that those who first-used before the age of 18 years were substantially more likely to develop a non-seminoma TGCT compared to never-users (adjusted OR: 2.80, 95% CI 1.60-5.10), but that those aged 18 or older were not (OR: 1.30, 95% CI 0.60-
This may suggest that any carcinogenic disruption of interest to the hypothalamic–pituitary–testicular axis occurs during (or before) puberty; however it is also possible that early initiation of cannabis exposure is a marker of other mediating factors, such as duration and frequency of cannabis use later in life. Another possibility is that since those cases that developed non-seminoma tumours were younger at the time of data collection than those who developed seminoma tumours, they may have been more likely to either recall or report marijuana use. Such a scenario would have the effect of exaggerating the association between cannabis use and non-seminoma development, while conversely attenuating the association between cannabis use and seminoma development. However, it should be noted that this inflation or attenuation would only occur if the age-matched controls who participated in these studies were not affected by this pattern of differential reporting by age – in other words, only if the cannabis use reported by controls was accurate. This is an area that warrants further exploration.”

Page 11, line 59: The evidence that it is "hormonal development" that is disrupted in utero is extremely weak. The authors should be more careful in their assessment of the research in this area.

Thank you for this comment. We agree that our statement here unnecessarily simplifies the complex (and obscure) aetiology of TGCT, and as such have amended the relevant section of text to read:

- “Best current evidence suggests that TC predisposition is determined prenatally; thus, it is possible that those who positively identify as current, chronic cannabis users are also more likely to have been exposed to cannabis during perinatal and/or early childhood development.”

Page 12, line 26: The report by Trabert et al. was a hospital-based, not population-based study.

Thank you for this correction.

Page 12, line 29: As noted earlier, not all of the studies used this process.

Thank you for this comment. We have revised the text accordingly, which now reads:

- “The three case-control studies examined for this review had strengths in a number of areas; however, each of the studies had acknowledged weaknesses, one of these being the ascertainment of cannabis exposure.”

Page 11, line 51: Please change "outcome" to "case or control".

We have amended the relevant text accordingly.

Also, the authors should amend this section to note that there is a major argument against this source of bias (as well as recall bias), and that is the fact that the association appears to be limited to a certain set of histologic types. It is unlikely that in these three studies that the
interviewers would have known the histology of the cases they were interviewing, and even if they did, it is difficult to fathom why interviewers would preferentially encourage certain answers for non-seminoma cases as opposed seminoma cases.

Thank you for this comment. We agree with the reviewer, and do not argue in the manuscript that interviewer bias impacted the results of the included studies – merely that since we do not know whether interviewers were aware of participant case/control status, it follows that we do not know whether interviewer bias either a) occurred, or b) impacted the observed associations. We believe this to be a fair assessment. However, we agree with the reviewer’s comment regarding seminoma vs. non-seminoma development, and have added text to that effect at the end of the relevant paragraph. The revised text now reads:

• “For all three studies, exposure to cannabis was measured using self-report – either during a face-to-face interview [8, 9] or on a written questionnaire.[7] According to the Newcastle-Ottawa Scale, one of the optimum mechanisms to measure exposure – and ostensibly minimise risk of information bias – is via a structured interview, where the interviewer is blinded to the case/control status of the participant. There is no record in any of the included studies that the interviewers were blinded to the status of the participant. The importance of this is that we do not whether (and to what extent) the association between cannabis exposure and TC was affected by interviewer bias (i.e. the interviewer knowing the case/control status of the participant, and inadvertently leading the participant toward certain answers). However, it would seem unlikely that interviewer bias could explain all of the observed associations between cannabis use and TGCT development; for example, it is difficult to imagine a scenario where knowledge of case/control status would cause interviewers to inadvertently lead those with non-seminoma tumours toward one response, and those with seminoma tumours to another.”

Page 12, line 53: Recall bias is not something that arises from lack of blinding of the interviewers to the case/control status of the subjects. It arises from the fact that the subjects themselves are not blinded to their own status. Please revise this paragraph accordingly.

Thank you for noticing this oversight. We have removed the statement regarding recall bias altogether from the section of text that discusses the lack of blinding of interviewers.

Page 13, line 17: The authors do not provide a justification for this assertion. Possibly they believe that because cannabis use was illegal in the regions in which the three studies were conducted, young men would tend to deny its use even if that were truly users. But some have argued that young men tend to be boastful about their activities, and might well overestimate their use of drugs (as well as other supposedly socially undesirable activities, such as sexual activity). I think the authors should consider what is really known about reporting of cannabis use and cite appropriate references.

Thank you for this comment. We have revised the relevant section of text to incorporate this suggestion:

• “…However the absence of a valid and easily-obtainable biomarker that does not involve the participant providing a urine sample may render such an approach untenable. It is
possible that the use of self-report only will underestimate current use of cannabis;[28-30] however there is also some evidence that self-report is an efficacious means of classifying current (or recent) exposure to cannabis among men of similar age to the participants of the three included studies.[31]

Even so, the issue at hand is the extent of misclassification of exposure due to self-report, and whether or not the misclassification is differential between cases and controls. If there is underreporting of exposure relative to the truth, and the underreporting is the same in cases and controls, then the ORs will be attenuated compared to the true association. Similar effects on the OR would happen if the cases and controls are equally over-reporting cannabis use. But if the misclassification is differential, then the ORs would not necessarily be attenuated. Importantly, the associations observed in the three studies could have occurred if the cases reported their cannabis use accurately but controls under-reported their cannabis use. Of course, as with the issue of differential response proportions (see below), for the results of these studies to have occurred, it would also have to be true that seminoma cases under-report cannabis use while non-seminoma cases accurately report such use. What reasoning could explain why patients with TGCT would differentially report cannabis use depending on their histology?

Thank you for this comment. We agree with the reviewer, and have revised the relevant section of text accordingly:

- “If the cases and controls are equally likely to either under- or over-report cannabis exposure, then the impact on the observed association between cannabis use and TGCT development would be likely to attenuate it. However, if TGCT cases are more likely to report/recall cannabis use than controls – because of concern that cannabis or similar exposures might be a cause of their cancer, or a similar reason – then this may serve to exaggerate the reported association away from the null. Of course, it is entirely possible that the same exaggeration could occur if cases reported their use accurately, but controls under-reported their use.”

As discussed with respect to a comment from Reviewer One, there is a plausible scenario in which recall bias might differentially affect non-seminoma and seminoma TGCT patients:

- “...Another possibility is that since those cases that developed non-seminoma tumours were younger at the time of data collection than those who developed seminoma tumours, they may have been more likely to either recall or report marijuana use. Such a scenario would have the effect of exaggerating the association between cannabis use and non-seminoma development. However, it should be noted that this exaggeration would only occur if the age-matched controls who participated in these studies were not affected by this pattern of differential reporting by age – in other words, if the cannabis use reported by controls was accurate.”

Page 13, line 28: This sentence is only partially correct. To be correct, the authors need to add the following after "who did not": "...and if the same differential is not present for the cases who responded and cases who did not respond,..."
We have made this amendment in the relevant text.

Page 13, line 28: The cannabis use data in these studies are not "rates" but rather, proportions or percentages.

We have made this amendment in the relevant text.

Page 13, line 47: I recommend that the authors revise this sentence to say "...the different potential sources of selection bias."

We have made this amendment in the relevant text.

Page 14, line 1: Each of the three studies provided data presented on quantity of cannabis use, and at least one of the studies showed that more frequent use (among current users) was more strongly related to risk than less frequent use. At the same time, the studies also show that high frequency users are not common in the population. Thus, there is already information in the published studies that addresses the concerns expressed by the authors in this sentence. For this reason, the authors need to revise this sentence.

Thank you for this comment. This paragraph specifically refers to the usefulness of ‘ever-use’ as a variable – not the wider usefulness of the studies under investigation, nor whether the included studies captured information that compensates for the shortcomings of this variable. As such, we would prefer to keep this paragraph as it is.

Page 14, lines 29-33: Most of the issues raised in this sentence have already been addressed to some extent by the published studies. For example, each study adjusted for potential confounders. In this respect, the authors have not made any cogent arguments that suggest that adjustment for confounding was a problem in the studies. This is also the first time in the manuscript that the authors use the term "mediators" and I recommend that they clarify what they mean (i.e., specific factors that they think are mediators, and/or why this is important to do). Also in this sentence, the mention of "use an evidence-based conceptualization" does not connect at all with anything else in the manuscript, and so it is unclear what the authors mean by it. In short, this sentence needs to be heavily revised.

Thank you for this comment – we agree with the reviewer that this concluding statement is unnecessary, and in-line with our response to comments made regarding the concluding statement in the abstract, we have removed it.

Table 2: The title of this table is lacking in important detail, such as what this particular meta-analysis is all about!

Thank you – we have revised the title of this table to:

- “Table 2: Papers included in meta-analysis of association between cannabis use and testicular cancer development, with study meta-data.”
Table 2: The meaning of the abbreviation in the "study design" column needs to be described in a footnote.

We have made this amendment in the relevant text.

Table 3: See comment regarding Table 2, as it also applies to this table.

Thank you – we have revised the title of this table to:

- “Table 3: Assessment of the quality of studies included in current meta-analysis against the Newcastle-Ottawa criteria.[17] Explanation of categorisations is presented in Additional File 2 alongside its corresponding number.”

Additional file 1: The title of this table has the same problem as the titles of tables 2 and 3.

Thank you – we have revised the title of this table to:

- “Additional File 1: List of papers excluded from the current meta-analysis following full-text screening, and the reason for their exclusion.”

Additional file 2: The title of this "file" has the same problems as the titles of Tables 2 and 3 and additional file 1.

Thank you – we have revised the title of this table to:

- Additional File 2: Detailed critique of manuscripts included in the current meta-analysis against Newcastle-Ottawa Scale criteria.

Figure 1: It is unclear from this figure how the number of papers decreased from 16 to 3. The figure needs to be revised accordingly.

Thank you – we have updated Figure 1 to include an additional box to clarify this point.

Figure 2a as well as other figures: Please spell out "Seminoma" and "Non-seminoma"

Thank you – we have reproduced these Figures accordingly.

Figure 2a: Please replace "Total" with "All histologic types."
Thank you for this comment – we would prefer to use the term ‘Total’ in this instance for the sake of brevity within the figure. We have, however, revised the figure legend to state that the term ‘Total’ refers to all histological types.

Reviewer #3:

Reviewer #3: This is a thorough systematic review and followed by a carefully conducted meta-analysis, with results describe in a well written report.

Thank you for this comment.

I have only a few suggestions:

(1) Page 7, lines 2-6: the authors indicate that cases and controls were matched on cryptorchidism and age; however they were not matched on cryptorchidism. The authors appear to appreciate this, because entries about this information in Table 2 are correct; I suggest revising the text accordingly.

Thank you for this comment. In line with a similar comment from Reviewer One, we have corrected the relevant section of text.

(2) Figure 2a: I suggest that authors describe (in results section) heterogeneity identified in analysis leading to these results, and comment (in discussion) on I likely source thereof.

Thank you for this comment. We agree with the reviewer, and have added the following text to the Results section of the manuscript:

• “In terms of heterogeneity, a high level of agreement between studies was found – with I2 values of 0% observed for most exposure variables (Figure 2b-d). A notable exception was the ever-use variable (Figure 2a), for which I2 values ranged between 59% (non-seminoma tumour type) and 71% (combined tumour types).”

And the following text to the Discussion section of the manuscript:

• “It is also worth noting that of all the exposure variables included in our meta-analysis, the greatest heterogeneity between studies was observed for the ever-use variable (I2 >50). The source of this heterogeneity is obscure and likely to be multifaceted – but could plausibly be due to heterogeneity between study populations in terms of a) pervasiveness of cannabis ever-use and/or b) willingness to report it. For example, fewer controls in the study by Trabert et al. (55%) [7] reported ever-use of cannabis compared to the study by Daling et al. (68%).[9]”

(3) Additional file 2, item 9: Cases who participated in the Trabert study were not from a registry of sorts, but rather a series of men with this diagnosis seen at a major medical center; please correct.
Thank you – we have amended the relevant text accordingly.

(4) Additional file 2, item 9: Cases who participated in the Lacson study were not from a registry of sorts, but rather from the Los Angeles Cancer Surveillance Program, which is a population-based cancer registry that is part of the SEER network: please correct.

Thank you – we have amended the relevant text accordingly.

Reference


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