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Cannabis with high cannabidiol content is associated with fewer psychotic experiences

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ABSTRACT

Objective: Cannabis is associated with psychotic outcomes in numerous studies, an effect that is commonly attributed to Δ ^{9}-tetrahydrocannabinol (Δ 9-THC). An increasing number of authors identify cannabidiol, another component of the cannabis plant, as an antipsychotic agent. The objective of the current study is to investigate the role of cannabidiol content in the association between cannabis use and psychiatric symptoms in a large non-clinical population of cannabis users.

Methods: In a web-based cross-sectional study we obtained detailed information about cannabis use and subclinical psychiatric experiences using the Community Assessment of Psychic Experiences (CAPE). Different types of cannabis (i.e. marijuana, hashish etc.) have distinctive proportions of Δ 9-THC and cannabidiol. Since average concentrations of Δ 9-THC and cannabidiol in the most popular types of cannabis sold on the Dutch market are annually measured, we were able to estimate exposure to Δ 9-THC and cannabidiol.

Results: We included 1877 subjects (mean age 23, SD 6.0) who used the same type of cannabis in the majority of the occasions (in >60% of occasions). We found a significant inverse relationship ($F(1,1877)$: 14.577, $p<0.001$) between cannabidiol content and self-reported positive symptoms, but not with negative symptoms or depression. The estimated effect size of cannabidiol content was small.

Conclusion: Although the observed effects are subtle, using high cannabidiol content cannabis was associated with significantly lower degrees of psychotic symptoms providing further support for the antipsychotic potential of cannabidiol.

1. Introduction

The association between cannabis use and psychotic outcomes is reported consistently, (Arseneault et al., 2004; Schubart et al., 2010; Moore et al., 2007; Skinner et al., 2010) although the causality of this association is difficult to assess and still under debate (Macleod et al., 2004; DeLisi, 2008). However, as cannabis is the most widely used illicit drug in the world (United Nations Office on Drugs and Crime, 2009), clarifying mental health sequelae of cannabis use is of great importance. A possible explanation of the heterogeneous nature of the findings in this field, is that exposure to cannabis is not uniformly defined and that several factors might influence biological exposure to cannabis. A number of effect modifying factors have already been identified. With an odds ratio of 2.09, a recent meta-analysis reported frequent use to be associated with psychotic outcome in general (Moore et al., 2007), moreover continued cannabis use might increase the risk on persistence of symptoms and therefore a psychotic disorder (Kuepper et al., 2011). Likewise, subjects who start to use cannabis early in life might also be more at risk to develop psychotic symptoms (McGrath et al., 2010; Schubart et al., 2010; Konings et al., 2008). Commonly, Δ ^{9}-tetrahydrocannabinol (Δ 9-THC) is denoted as the main psychoactive ingredient of cannabis products such as marijuana and hashish (Mechoulam and Gaoni, 1965) and the concentration or content of Δ 9-THC is traditionally considered as the main measure of cannabis potency (McLaren et al., 2008). However, cannabis plants contain more than 70 different cannabinoids that are also found in the cannabis products on the market (Elsohly and Slade, 2005). Cannabidiol is one of these cannabinoids and a number of studies suggest that cannabidiol has antipsychotic properties and could therefore modify the mental health sequelae of cannabis use. (Morgan and Curran, 2008; Leweke et al., 2000; Zuardi et al., 1995, 2006b). Di Forti et al. found that the use of cannabis containing a high Δ 9-THC- and a low cannabidiol (CBD) concentration was retrospectively associated with a higher risk of a first psychotic episode (Di Forti et al., 2009). Similarly, a number of authors hypothesize that cannabidiol possibly antagonizes the effects of Δ 9-THC (King, 2008; Smith, 2005; McLaren et al., 2008); i.e. that it has protective properties against psychosis.

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Concentrations of cannabidiol and Δ 9-THC differ greatly between various types of cannabis products such as marijuana (weed) and hashish (resin), year and by place of origin (Potter et al., 2008; Trimbos, 2008, 2009; Mehmedic et al., 2010). For instance, in 2008 marijuana produced in The Netherlands contained virtually no cannabidiol and had a mean Δ 9-THC concentration of 16%, whereas hashish imported from countries as Nepal, Afghanistan or Morocco, contained a similar concentration of Δ 9-THC (17%) but also contained 9% of cannabidiol (Trimbos, 2009). Given the hypothesized antipsychotic potential of cannabidiol, the variation in concentrations of cannabidiol could be reflected in a moderation of the association between cannabis use and psychotic symptoms. Further exploring the role of cannabidiol in the association between cannabis and psychosis symptoms could be of value in the debate on the impact of cannabis on population mental health. Moreover, evidence on the associated risks of particular cannabis products could improve the quality of psychoeducation on the risks of cannabis use.

This study aims to investigate the influence of the Δ 9-THC/cannabidiol ratio in different cannabis products on the association between cannabis use and psychiatric symptoms in a large non-clinical population of young adult cannabis users.

2. Materials and methods

2.1. Participants

Participants were recruited using a project website launched in 2008 (www.cannabisquest.nl). Individuals were directed to the website via different media; advertisements distributed on more than 100 different collaborating colleges and universities using intranet, posters and flyers. The chance to win an Apple iPod ® or an Nintendo Wii® was used as an incentive. The website targeted mainly Dutch speaking young adults and adolescents (18–25 years). Besides personal information as age, educational level and contact details, all participants filled out the Community Assessment of Psychic Experiences (CAPE)(Stefanis et al., 2002; Konings et al., 2006) and the Cannabis Use Inventory (CUI) (described below). Only subjects who indicated to use cannabis were included in the analyses. Participants who indicated having an inconsistent pattern of cannabis use (<60% consistent preference) or were not aware of the type of cannabis they used, were excluded from the analyses. Verification questions were used to protect against random answers and internet bots that run automated tasks. To increase the homogeneity of the sample participants who indicated to be younger than 10 years or older than 60 years of age were excluded.

This study was approved by the UMC Utrecht medical ethical commission and all participants gave online informed consent.

2.2. Assessment of psychiatric symptoms

The CAPE is a 42-item, self-rating instrument and measures experiences from three symptom dimensions: positive-, negative- and depressive symptoms with discriminative validity in individuals from the general population (Stefanis et al., 2002; Konings et al., 2006).

2.3. Cannabis quantity measure

To assess detailed information on cannabis use the Cannabis Use Inventory (CUI) questionnaire was developed. The CUI offers a retrospective comprehensive inventory of life time cannabis exposure. Participants are asked to indicate at which age they started to use cannabis and in which frequency. Thereafter subjects are asked to indicate if, and if so at what age, their consumption frequency had changed significantly and how long this period lasted. In total, participants can indicate five different periods of distinct cannabis use frequency, covering the period since first use until present day. Based on information from the CUI, the population sample was arbitrarily divided in nine categories on quantity of cannabis use in the last year: 1) Once a year or less, 2) Over once a year but not monthly, 3) Once a month, 4) Weekly for 0 to 5 euros a week, 5) Weekly for 5 to 10 euros a week, 6) Weekly for 10 to 25 euros a week, 7) Weekly for 25 to 50 euros a week, 8) Weekly for 50 to 100 euros a week, 9) Weekly for more than 100 euros a week. Outliers in amount of use (more than two standard deviation from the mean equalling) were excluded from analysis.

2.4. Annual reports on Δ 9-THC and cannabidiol content

The Netherlands Institute of Mental Health and Addiction (Trimbos Institute) is a Dutch centre of expertise and conducts research on mental health, mental resilience and addiction. Since 1999, the Trimbos Institute annually visits a random selection of 50 Dutch Coffeeshops (establishments were the distribution of small quantities of cannabis for personal use is legal under Dutch law), for reference, approximately 700 Coffeeshops existed in The Netherlands in 2007 (Bieleman et al., 2008). The researchers measured the concentrations of Δ 9-THC, cannabidiol and cannabinol in the following five cannabis products: i) Dutch marijuana, ii) imported marijuana, iii) Dutch hashish, iv) imported hashish and v) the strongest marijuana sold in the Coffeeshop (Trimbos, 2009). Since all subjects in the current analysis had indicated the type of cannabis product they commonly use, the average measurements mentioned in the annual Trimbos reports, were used as a by proxy estimate of exposure to these cannabinoids.

2.5. Cannabis type

Following the categorization of the annual Trimbos Institute measurements as described above, we asked participants which of the following types of cannabis they usually consumed; 1) Dutch marijuana, 2) imported marijuana, 3) Dutch hashish, 4) imported hashish, 5) the strongest type in my Coffeeshop. To increase the validity of our classification, participants could also give the following answers 6) hashish of unknown origin, 7) marijuana of unknown origin, 8) the most popular type in my Coffeeshop, 9) variation between two types 10) different every time, and finally 11) unknown. Only those participants were selected for further analysis who indicated using one of the cannabis types that are represented in the annual Trimbos Institute report (types 1,2,3,4 and 5). Finally, participants were asked how often they used the selected type of cannabis. We excluded subjects if they indicated using the selected type in less than 60% of the occasions where they used cannabis. Combining information from the Trimbos Institute annual reports on cannabinoid concentrations and the individual cannabis use patterns in our dataset, we were able to estimate the exposure to Δ 9-THC and cannabidiol. A Δ 9-THC/cannabidiol ratio was calculated for each participant.

As a result of different THC and cannabidiol concentrations in the five cannabis products in the years 2008 and 2009, ten (5×2) levels THC/cannabidiol concentrations were calculated within the sample (THC/cannabidiol concentrations: 2.0, 3.6, 8.8, 16.0, 24.8, 29.6, 45.8, 55.3, 75.0, 81.5).

To avoid analyses of small groups and in order to conserve power we applied a median split to dichotomize the THC/cannabidiol ratio given that these cannabidiol concentrations broadly fall into two categories (high and low THC/cannabidiol ratio). Median split was at 55.3 effectively defining a high cannabidiol content group and a low cannabidiol group that were used in the final analyses.

2.6. Statistical analysis

Firstly, analysis of Co-Variance (ANCOVA) was used to investigate the association between the degree of cannabidiol content (high/low) and the total CAPE score, adjusting for age, sex and initial age and amount of cannabis use. Secondly, a MANCOVA was used to analyze the impact of cannabidiol content (dichotomized THC/cannabidiol ratio) on the association between cannabis use and the three CAPE symptom dimensions (positive, negative and depressive) jointly as outcome measures, likewise adjusting for age, sex and initial age and amount of cannabis use. Additionally a four linear regression analyses were performed using the total cape score, positive-, negative and depressive symptoms as dependent variables and the undichotomized THC/CBD ratio as main independent variable adjusting for age, gender, age at first use and amount of cannabis use.

3. Results

3.1. Sample characteristics

We included a total of 1877 participants selected from an initial number of 11,465 subjects that filled out the online questionnaires in the period from April 2008 until March 2010. The reasons for exclusion were; not using cannabis (32%), not knowing exactly which type of cannabis was used (31%), incorrect answers to verification questions (16%), an inconsistent pattern of cannabis use (2.8%) and miscellaneous reasons (1.4%). The mean age of the participants was 23 years (SD: 6.0) of which 34% was female. Three percent of the sample had no educational diploma, 43% had a secondary school diploma as highest academic achievement, 38% had a non-academic post-secondary diploma and 10% had a University degree. The mean cape score in this sample was 111.0 (SD: 31.7) which is higher than in a sample of non-clinical, cannabis naïve young adults as described elsewhere (Schubart et al., 2010).

3.2. Cannabis use preferences

The majority of the sample preferred “Dutch marijuana” (69%),”Imported Hashish” was second (18%) followed by the “ strongest marijuana available” (8%) and ”Dutch Hashish” (3%). After the median split, the low cannabidiol content cannabis use group ($n=663$) is composed of 595 users who prefer “Dutch marijuana” in 2009 (THC: 15.0%, CBD: 0.2%) and 68 subjects who preferred the “strongest marijuana available” in 2009 (THC: 16.3%, CBD: 0.2%). The high cannabidiol content group ($n=1214$) consisted of 707 subjects who preferred “Dutch marijuana” in 2008 (THC: 16.6%, CBD: 0.3%), 25 subjects who prefer “ Imported marijuana” (THC: 6.4%, CBD: 0.4%), 57 subjects who use “ Dutch Hashish” (THC: 26.6%, CBD: 0.9%), 345 individuals that consistently used “imported hashish” (THC: 17.9%, CBD: 8.8%) and 80 subjects that preferred “strongest marijuana available” in 2008 (THC: 16.6%, CBD: 0.4%). As shown in Table 1, the average percentage of preference of a single type of cannabis and the amount of cannabis used was comparable between the two groups. Cannabis preference was correlated with age and gender, but post-hoc analysis revealed no significant differences between the user groups.

3.3. Cannabis use and CAPE scores

After adjusting for age, gender, amount of cannabis use and age of first use, the THC/CBD ratio had a significant effect on total CAPE score. Subjects who use cannabis with a low THC/CBD ratio had significantly lower total CAPE scores than subjects that preferred cannabis types with a high THC/CBD ratio ($F(1,1877)$:5.182, p: 0.023), albeit with a small effect size (Partial Eta^2: 0.003). Fig. 1 shows the estimated marginal means of total cape scores in subjects that use high or low cannabidiol containing cannabis types. A multiple analysis of covariance (MANCOVA) showed a positive and significant relationship between the quantity of cannabis use in the last year and the outcome on all three dimensions of the CAPE, (Pillai's trace F: 3.303, p: 0.001).

The age at onset of cannabis use was not associated with the total CAPE ($F(1,1877)$: 0.578, p: 0.447) or with the CAPE sub scores (Pillai's trace F: 0.004, p: 0.055) most likely due to the absence of an effect on the negative and depressive symptoms (between group effect, negative ($F(1,1877)$: 0.142, p: 0.706), depressive ($F(1,1877)$: 0.014, p: 0.905)) in the presence of an effect on positive symptoms only ($F(1,1877)$: 4.809, p: 0.028) consistent with our previous findings (Schubart et al., 2010).

3.4. CBD content and CAPE scores

A multiple analysis of covariance (MANCOVA) with the three CAPE sub scores (positive, negative and depressive symptoms) as outcomes, showed a significant effect of cannabidiol content (Pillai's trace F: 5.691, $p=0.001$). Participants who indicated using cannabis types with high cannabidiol content reported significantly less positive symptoms ($F(1,1877)$: 14.577, $p<0.001$) again with small effect size (Partial Eta^2:0.008). Fig. 2 shows the estimated marginal means of the relationship between cannabis exposure and CAPE outcome for the high and low cannabidiol content groups. The associations of cannabidiol content with negative and depressive symptoms were not significant (negative ($F(1,1877)=0.366$, p: 0.545) and depressive ($F(1,1877)$: 1.971, p:0.161)). See Table 1. The amount of use was independently associated with the total CAPE score (Pillai's trace F: 0.048, p: 0.000) and between group effect (F:8.853, $p<0.001$). Finally linear regression analyses showed that the THC/CBD ratio of preferred types of cannabis, after adjustment for age, gender, age at first use and frequency of use, is only associated with positive symptoms (β: 0.052,

Table 1
Characteristics of the cannabidiol content groups and results of the analyses.

Group characteristics	High CBD	Low CBD		
N	1214	663		
Mean age (SD)	23.1 (4.4)	24.3 (7.0)		
% male	67%	64%		
CBD/THC ratio's	2.0, 3.6, 8.8, 16.0, 24.8, 29.6, 45.8, 55.3	75.0, 81.5		
Cannabis type loyalty[a]	85%	86%		
Median cannabis use category	1×/month	Weekly<€5		
Outcome[b]			*F*	*p*-value
Mean CAPE Total (SD)	109.8 (31.5)	112.8 (33.6)	5.182	0.023
Mean Positive (SD)	39.7 (12.8)	41.7 (14.5)	14.577	<0.001
Mean Negative (SD)	45.5 (15.5)	45.9 (16.0)	0.366	0.545
Mean Depressive (SD)	24.6 (8.9)	25.1 (9.1)	1.971	0.161

[a] Loyalty is defined as the mean percentage of the cases in which the participants choose their cannabis type of preference.
[b] All analyses were adjusted for age, gender, amount of cannabis use and age of first cannabis use.

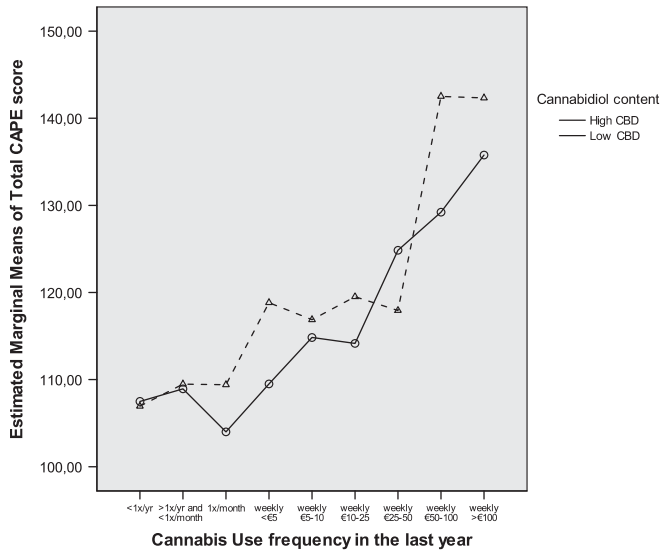

Fig. 1. Mean total CAPE score and cannabis exposure per cannabidiol content group ($n = 1877$).

$p<0.001$) as opposed to negative symptoms (β: 0.004,p: 0.850), depressive symptoms (β: 0.031,p: 0.178) and the total CAPE score (β: 0.031,p: 0.155).

4. Discussion

In a large cross-sectional sample of cannabis users from the general population, we investigated the association between cannabidiol content of preferred cannabis types and self-reported positive-, negative- and depressive psychiatric experiences. A subtle but significant association between using a cannabis product with low cannabidiol content and high levels of psychotic symptoms was observed. In contrast, low cannabidiol content was not associated with differences in negative or depressive symptoms. Our findings support earlier reports that attribute a role to cannabidiol in modifying the impact of Δ 9-THC on the risk of various psychotic outcomes.

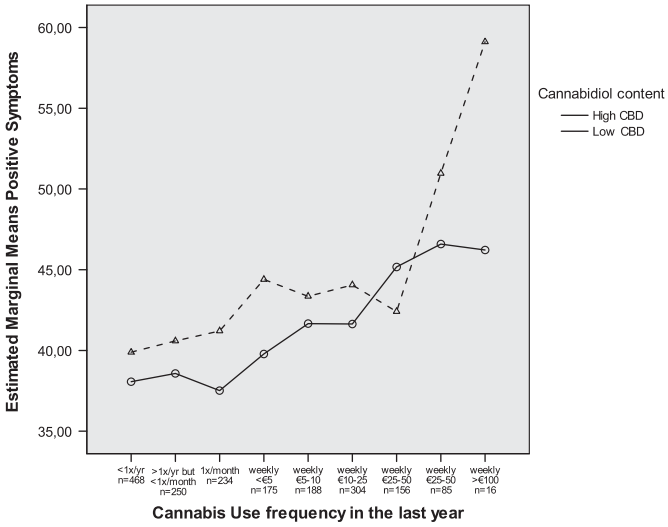

Fig. 2. Mean score on positive symptoms and cannabis exposure per cannabidiol content group ($n = 1877$).

4.1. The relationship between CBD and psychotic symptoms

The hypothesis that cannabidiol impacts on the effect of Δ 9-THC was firstly postulated by Rottanburg et al. (1982) who found an increased prevalence of psychotic disorders among users of cannabis with high Δ 9-THC content and lack of cannabidiol. Zuardi et al. (1982). observed that cannabidiol, co-administered with Δ 9-THC, significantly reduced the psychotomimetic symptoms induced by Δ 9-THC. A later study, using binocular depth inversion as a psychosis model, reported cannabidiol to attenuate the effects of a synthetic Δ 9-THC cannabinoid, Nabilone, suggesting cannabidiol has antipsychotic properties (Leweke et al., 2000). Moreover, recently a series of papers was published on distinct effects of CBD and THC on various measures of brain function, generating an explanatory hypothesis for the phenomenological differences associated with these two cannabinoids (Bhattacharyya et al., 2010; Fusar-Poli et al., 2010).

The findings of the current study also concur with the results of Di Forti et al. who report an association between the use of cannabis with high THC and low cannabidiol content and a higher risk of developing a first psychotic episode (Di Forti et al., 2009) and a previous study in a small non-clinical population that showed that in hair samples of 140 individuals, the measured cannabidiol/Δ 9-THC ratio was associated with the report of schizophrenia-like symptoms (Morgan and Curran, 2008), with low ratio's predicting high levels of symptoms.

4.2. Strengths and limitations

Although the observed effect of CBD on the level of positive symptoms is significant, the effect sizes in our study are small compared to earlier studies investigating the antipsychotic potential of cannabidiol. A possible explanation of this small effect size might be that the dosage of cannabidiol in cannabis products intended for smoking is much lower than in the purified oral form that is used in treatment studies. The highest median cannabidiol concentration measured in cannabis samples, was 8.8% (Trimbos, 2008). Estimating that a joint contains 1 g of hashish, this would equal 88 mg of cannabidiol, which is 10 times less than applied in earlier treatment studies (Zuardi et al., 2006a; Leweke et al., 2000). Moreover, the therapeutic properties of cannabidiol are most probably further reduced by the burning process that occurs when cannabis is smoked. Furthermore, the cannabis products used by the subjects in our study are not actually the same samples in which cannabinoid concentrations were measured. Although this clearly constitutes a measurement bias, the fact that a small albeit significant effect was still found, further underlines the potential antipsychotic properties of CBD. Since the design of the current study is cross-sectional, causal inference on the reported association is not possible and reversed causality may partially account for the reported findings. An alternative explanation for the current findings therefore, is that individuals in the general population who experience psychotic symptoms are more likely to prefer cannabis products with lower cannabidiol content. Although this may not be the most intuitive explanation, it cannot be ruled out. A prospective, longitudinal design, accounting for baseline psychotic symptoms and genetic (family) risk of psychosis, could thoroughly assess the temporal dynamics between psychotic symptoms and exposure to THC and cannabidiol. Another potential limitation of the current study is that all data was collected using the internet. The increased availability of internet access and the development of better web-based tools have improved the possibilities to acquire information on psychiatric symptoms via the internet. Web-based tools are therefore considered a valid additional method in epidemiological research. However, as discussed in several critical reviews on the use of online tools, the use of web-based assessments can potentially lead to inaccuracy (Meyerson and Tryon, 2003; Balter et al., 2005; Gosling et al., 2004; Ekman et al., 2006). The distribution of this potential inaccuracy however, is most likely independent of the type of

cannabis used (exposure measure) and is therefore unlikely to have systematically influenced the reported associations. Moreover, the sample is comprised of cannabis users only and therefore is a selected sample by definition. We also only included subjects with consistent and explicit preferences of cannabis use. However, by adjusting our statistical model for age, gender and cannabis use, the risk of confounding due to selection within the sample is minimized.

Furthermore, a median split was applied to avoid separate analyses of groups with small numbers of subjects. The use of a median split has potential disadvantages, since all values on each side of the median are collapsed, information is lost. However since the distribution of the CBD ratio's is not normal and the small group sizes lead to reduced power, a median split is a necessary mean to preserve power. Finally, concomitant use of other drugs than cannabis was not measured and could potentially have influenced our results.

4.3. Conclusion

To our knowledge this is the first large study to investigate the influence of cannabidiol content on the presence of psychiatric symptoms in cannabis users from the general population. The key finding of the current study is that cannabidiol mitigates the psychotic symptoms associated with cannabis use with a small, albeit significant, effect. Given the low dose of cannabidiol in joints as compared to oral administration in treatment studies, a larger effect could not be expected. The current data add to our knowledge of cannabidiol as a potential antipsychotic agent, suggesting that cannabis types with high cannabidiol content are significantly less strongly associated with psychotic symptoms.

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Contributors

Christian Schubart, was involved in the conceptualization and design of the study, collecting and interpreting the data and drafting the paper.

Iris Sommer participated in the conceptualization and design of the study, data interpretation and critical revision of the draft.

Willemijn van Gastel performed literature search, statistical analysis and critical revision of the draft.

Rogier Goetgebuer was involved in the literature search the statistical analysis of the data and drafting the paper.

René Kahn was involved in the design of the study, interpretation of the data, revision of the draft and supervision of the project.

Marco Boks was involved in the design of the study, interpretation of the data, revision of the draft and supervision of the project.

All authors contributed to and have approved the final manuscript.

Conflicts of Interest

This study was financially supported by a Grant of the NWO (Netherlands Organization for Scientific Research), Grant number: 91207039. None of the authors of the above manuscript has any conflict of interest which may arise from being named as an author on the manuscript or receives any financial support that could potentially affect the reporting of the study.

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