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ORIGINAL ARTICLE

Conscientiousness and Medication Adherence: A Meta-analysis

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Abstract
Background Approximately a quarter to a half of all people fail to take their medication regimen as prescribed (i.e. non-adherence). Conscientiousness, from the five-factor model of personality, has been positively linked to adherence to medications in several recent studies.
Purpose This study aimed to systematically estimate the strength and variability of this association across multiple published articles and to identify moderators of this relationship.
Method A literature search identified 16 studies (N=3,476) that met the study eligibility criteria. Estimates of effect sizes (r) obtained in these studies were meta-analysed.
Results Overall, a higher level of conscientiousness was associated with better medication adherence (r=0.15; 95 % CI, 0.09, 0.21). Associations were significantly stronger in younger samples (r=0.26, 95 % CI, 0.17, 0.34; k=7).
Conclusion The small association between conscientiousness and medication adherence may have clinical significance in contexts where small differences in adherence result in clinically important effects.

Keywords Adherence · Compliance · Personality · Conscientiousness · Medication

Introduction

Most long-term medical treatments for chronic illness involve the prescription of a regimen of one or more daily medications [1]. It has been estimated that between 25 [2] and 50 % [3] of patients do not follow medical recommendations as prescribed. This has been termed *non-adherence* and is a primary cause of the existence of considerable efficacy–effectiveness gaps for many evidence-based medical treatments [4]. Non-adherence to medication is a complex behaviour with many diverse determinants ranging from the micro-level of individual patient beliefs about medications [5] or the complexity of the specific medical regimen [6] to the macro-level of health care organisational factors [7, 8]. One intriguing and recurring psychological explanation for the failure to follow medical advice concerns the role of personality characteristics [9–11].

There has been a particular focus on conscientiousness, one of the traits of the 'Five-Factor model' of personality [12, 13], with respect to the self-regulation of health-relevant behaviour [14]. Conscientiousness is defined as 'socially prescribed impulse control that facilitates task-and goal-directed behaviour, such as thinking before acting, delaying gratification, following norms and rules and planning, organising and prioritising tasks' ([15], p. 121). This definition has clear resonance with a number of non-trait psychological constructs relating to volitional processes that dominate the health behaviour change literature, such as action control [16] and self-regulatory strength [17, 18]. Bogg and Robert's meta-analytic review [19] of conscientiousness and health behaviour indicates that conscientiousness is reliably associated with a range of both positive and negative behaviours that are known to be important for health and the onset of range of diseases, namely tobacco use, diet and activity patterns, excessive alcohol use, violence, risky sexual behaviour, risky driving, suicide and drug use [19].

A recent theoretical model examining the central role of traits to the disease process, suggests that disease process is influenced by health behaviours, cognitions and adherence to medical treatment [9], with traits important to the expression of these variables. In the same way that conscientiousness is a good candidate trait for the prediction of key primary prevention health behaviours [19], it should also

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be a good candidate trait for the prediction of secondary prevention behaviours such as medication adherence [9]. Despite the systematic study of the relationship between conscientiousness and medication adherence for almost 20-years [20], there has been no systematic evaluation of strength and variability of its contribution.

Medication taking is a qualitatively different behaviour from those examined by Bogg and Roberts [19] in at least three key respects. First, medication taking is not a behaviour that typically occurs in an interpersonal context in the way that many of the health behaviours do [19]. Such behaviours are often relatively prolonged social interactions (e.g. eating, physical activity and alcohol use) and are social interactions by definition in some cases (e.g. risky sex and violence). Second, medication taking is more often a secondary prevention behaviour in individuals where disease has been confirmed and some illness has been experienced and the aim of the medication regimen is to reduce the risk of reoccurrence of the illness or to alleviate symptoms [1]. Third, medication taking does not typically provide immediate and automatic hedonic benefits in the way that physical activity, alcohol use, unhealthy eating, smoking, risky sex and violence do. These behaviours may be more susceptible to automatic and impulsive processes [21, 22] whereas medication taking may be more strongly driven by reflective processes [23]. Therefore, the nature of the observed associations between conscientiousness and the health behaviours identified in the Bogg and Roberts review [19] cannot be assumed for medication taking.

However, there are key aspects of conscientiousness that also make it a good candidate for increasing levels of medication adherence that may be more reflective, long term and routinised. Conscientiousness is linked to planning and impulse control via diligence, perseverance, tenacity, orderliness and industriousness [24–26]. These are all qualities that are likely to be helpful with respect to remembering and planning to take medications, and also paying attention to doses and times of mediation [27]. Consistent with this conscientiousness has been shown to enhance performance on a number of cognitive and social cognitive variables linked to persistence, memory, vigilance and planning. For example, those high in conscientiousness perform better on memory tasks [28], training and transfer of training [28], attention and executive control task [24], vigilance tasks and perceptual speed [29, 30], show increased effort [31] and are more likely to enact their intentions [32]. Thus, conscientiousness in particular should influence adherence and that the main route of this influence would be through their effects on basic cognitive and social cognitive processes [9].

To date, there has been no systematic attempt to quantitatively synthesise the evidence linking conscientiousness and adherence to medication across the range of studies and methodologies that have looked at this issue. In the present study, we identify studies that have estimated the association between conscientiousness and medication adherence and perform a meta-analysis on this data to estimate the strength of this association and to identify moderators of this association. It is likely that the effects of conscientiousness on medication adherence vary according to a range of methodological factors. Therefore, we also conducted moderator analyses, which were informed by previous meta-analyses examining the association between psychological factors and adherence to treatment [33, 34].

Method

Search Strategy

ISI Web of Science (ISI WOS), PubMed and PsychInfo were searched for full published reports to the end of August 2012. The reference lists of selected studies were also searched for additional articles. The following three search strings were used initially: (1) conscientiousness and adher*, (2) conscientiousness and complian* and (3) conscientiousness and medication. We also conducted searches using the nine facets of conscientiousness identified in a recent narrative review by Bogg and Roberts [13] with the terms ‘Personality’, ‘adher*’, ‘complian*’ and ‘medication’. These facet terms were ‘orderliness’, ‘industriousness’, ‘self-control’, ‘responsibility’, ‘traditionalism’, ‘decisiveness’, ‘formality’, ‘punctuality’ and ‘persistence’. In addition citation searches within ISI WOS were performed on all papers that met the criteria for study inclusion. The search strategy was developed to identify papers examining conscientiousness as defined by the Big 5 approach [15].

Criteria for Study Inclusion

The following criteria were used to determine study inclusion: (1) The published paper was written in English, published in full-text format in a peer-review journal, and analyses were of primary data. (2) A measure of medication adherence was included using any of the following methods: self-report, serum assay, pill count, refill or prescription records and electronic monitoring. (3) A measure of conscientiousness, as defined by the Big 5 approach [15] or similar, was included. (4) A measure of the strength of the association between conscientiousness and medication adherence was included or a statement that an association did not exist was specified.

Data Extraction

An a priori data extraction form was developed, and data were coded from each paper by two coders. Any discrepancies in

coding were identified and resolved by rechecking the given paper and referring to established methodological conventions in meta-analysis [35]. The following information was extracted from each included study: the study sample size, the medical condition associated with the prescribed medications, the study design, the methodology used to measure medication adherence, the measure used to assess conscientiousness, the sample demographic characteristics and the bivariate correlations (or related statistical information) between Conscientiousness and medication adherence.

Study Quality Assessment

Each study was assessed for study methodological quality using a 4-point assessment tool developed for this meta-analysis by two coders. Any discrepancies in scoring were identified and resolved by rechecking the given paper and referring to the preset criteria for assessing study quality. A point was given for each of the following four methodological criteria achieved. (1) A prospective design: this can reduce biases in effect sizes due to contemporaneous measurement of conscientiousness and medication adherence, e.g. focusing illusion effects [36]. (2) An objective measure of medication adherence was used, i.e. a measure that did not rely on self-report, as social desirability and recall biases could be minimised. (3) A sample size greater than 85 was recruited, as this is the minimum number required to have 80 % power to detect a medium effect size using r and an alpha of 0.05 [37]. This would increase the likelihood that a more reliable estimate of the association was ascertained. (4) An adjustment for age was included in the estimation of the effect size of the association of conscientiousness and medication adherence, as there is evidence that conscientiousness increases in older adulthood [38] and poorer medication adherence has been linked to age [39]. Therefore analyses that adjust for age can remove that part of the association between conscientiousness and medication adherence that may be due to developmental processes (e.g. poorer adherence in early and later life).

Statistical Analysis

The *r* effect size of the association between conscientiousness and medication adherence from each study was used as the primary data for the meta-analysis. This represents the strength and direction of association between the measures of adherence and the measure of conscientiousness. Positive effect sizes reflect the association of better adherence (i.e. lower non-adherence and higher levels of conscientiousness). Comprehensive Meta-analysis Version 2 software © was used to convert effect sizes into *r* when they were not presented in the included paper. A random effects model was used for all analysis and plots unless otherwise stated. Unadjusted *r* was used in all studies when available ($n=13$). When a non-significant association was reported but no data was available, $z=0.00$ was assigned as a conservative estimate. This was done for two studies [40, 41]. When studies used multiple measures of adherence [42] and examined several outcomes, these data points were averaged. This conservative approach has been advocated and applied in previously published meta-analytic reviews in this area [33]. When studies reported varying sample sizes for reported statistical tests the smaller sample size was used.

In order to assess the potential role of moderators in the medication adherence and conscientiousness relationship, each study was coded according to the following: sample size, study design (cross-sectional/ prospective) whether self-report only was used to measure adherence (yes/no), whether the sample was defined as a patient i.e. a particular medical diagnosis or a 'healthy' group i.e. primary preventive medications (yes/no), whether the NEO was used (to examine the observed associations in those studies with a homogeneous set of conscientiousness scales), study quality (0–4 scale) and average age of the sample, which was also examined as a categorical moderator (< and >50 years old). The selection of these moderators was based on previous meta-analyses of psychological factors and medication adherence [33, 34]. Publication bias was assessed both schematically using a funnel plot and statistically using Egger's regression intercept and by calculating the failsafe number-FSN [35].

Results

Identified Studies

In total, 580 unique records were initially screened from using the search terms in the three databases. The most common reasons for paper exclusion were no medication adherence measure and no primary data. Following the assessment of these studies for eligibility and the citation searches of the detected eligible studies 16 papers were identified based on the criteria for study inclusion set out in the method section. The sixteen papers were published over a 17-year period between 1995 and 2012. The mean study quality score on the 0–4 study quality scale that assessed study design, adherence measurement, sample size and statistical adjustment for age was 1.81 with a standard deviation of 0.75 and a range of 1–3.

Meta-analysis

Table 1 presents details of the study characteristics included in the meta-analysis. The median sample size was 108 with a range of 55 to 771. Fourteen out of the 16 samples (88 %)

Table 1 Study characteristics

Reference	Sample size	*r*	Controls	Medical condition	Study design	Adherence measure(s)	Conscientiousness measure	Mean age (years)	Study quality score
Axelsson et al. [74]	109	0.187	None	Asthma	Cross-sectional	Self-report	Impulsivity from HP5i	22	1
Axelsson et al. [75]	749	0.162	None	Chronic disease	Cross-sectional	Self-report	NEO-FFI	53.59	1
Bruce et al. [42]	55	0.340	None	Multiple sclerosis	Prospective (8 weeks)	Electronic monitoring, diary and self-report	NEO-FFI	43.36	2
Christensen et al. [55]	107	0.320	None	Type I diabetes mellitus	Cross-sectional	Self-report	Big 5 inventory	41.7	1
Christensen and Smith [20]	72	0.270	None	Renal dialysis	Prospective-(8 weeks)	Serum assay of phosphorus	NEO-FFI	46.39	2
Cohen et al. [40]	65	0.000	None	Depression	Prospective (14 weeks)	Electronic monitoring	NEO-PI-R	41.2	2
Dobbels et al. [76]	174	0.175	None	Heart, liver and lung transplant candidates	Cross-sectional	Self-report	NEO-FFI	52.3	1
Ediger et al. [77]	326	0.050	Age, gender, employment, diagnosis, gender*age, gender*diagnosis and gender*employment	Inflammatory bowel disease	Prospective (1 year)	Self-report	NEO-FFI	41	3
Insel et al. [78]	58	0.260	None	Community-dwelling older adults who were self-administering medications	Prospective (8 weeks)	Electronic monitoring	SFPQ-industriousness	77	2
Jerant et al. [79]	771	0.010	Neuroticism, agreeableness, extraversion and openness	Community-dwelling older adults who were participating in a RCT	Prospective (median, 6.1 years)	Pill counts	NEO-FFI	78.6	3
Moran et al. [80]	56	−0.090	Previous transplant failure, social support and the interaction term for social support and C	Hemodialysis	Prospective (8 weeks)	Serum assay of phosphorus	NEO-FFI	57.2	2
O' Cleirigh et al. [53]	91	0.370	None	HIV positive	Prospective (1 year)	Self-report	NEO-FFI	37.9	2
Penedo et al. [41]	116	0.000	None	HIV/AIDS	Cross-sectional	Self-report	NEO-PI-R	39.2	1
Quine et al. [81]	537	0.150	None	Hypertension	Prospective (8 weeks)	Self-report	International personality item pool	69	2
Stilley et al. [82]	158	0.240	None	LDL serum cholesterol levels of 160 mg/dl or higher	Prospective (24 weeks)	Electronic monitoring	NEO-PI-R	46.2	3
Wiebe and Christensen [83]	65	0.040	None	Hemodialysis	Prospective (8 weeks)	Serum assay of phosphorus	NEO-FFI	56	1

HP5i The Health-Relevant Personality 5 Factor Inventory, *NEO-FFI* The Neuroticism, Extraversion, and Openness to Experience, Five Factor Inventory, *NEO-PI-R* The revised NEO Personality Inventory, *SFPQ* Six-Factor Personality Questionnaire, *C* Conscientiousness

were chronic illness samples. Eleven out of the 16 samples were prospective studies (69 %). Eight of the studies (50 %) used self-report methods only to measure medication adherence. Twelve studies (75 %) used versions of the NEO to measure conscientiousness. The mean age of the study samples was 52.63 (SD=16.33).

The overall average weighted correlation coefficient across the 16 studies was r=0.12 (p<0.001) using a fixed effects model and r=0.15 (p<0.001) using a random effects model, which is presented in the forest plot in Fig. 1. This figure represented as an odds ratio using the random effects model was 1.71 (95 % CI, 1.37, 2.14) and 0.30 (95 % CI, 0.17, 0.42) represented as a standardised difference in means. Post hoc power analysis reveals that a sample size of 346 would be required to have 80 % power to detect an effect of this size with a two tailed alpha level of .05. Only three studies therefore were adequately powered to detect this size of an effect. The effect was robust with the failsafe N calculated as 217 null studies required to make the p value greater than 0.05. There was significant moderate heterogeneity around the mean effect size in the observed studies (Q=38.37, p<0.01; I^2=60.90). Figure 2 presents a funnel plot of the effect sizes observed in the included 16 studies. Egger's regression intercept indicated no evidence for publication bias in the identified studies (1.13; 95 % CI, −0.67, 2.92; p=0.20).

Meta-Regression Analyses

Random effects meta-regression, using the moment method [35], revealed that larger sample sizes (Z=−1.21, p=0.22) and higher study methodological quality (Z=−0.80, p=0.42) were not associated with observed effect sizes. An older sample average age (Z=−2.11, p=0.03) was associated with significantly smaller effect sizes.

Categorical Moderators

Table 2 provides a summary of the meta-analysis by potential categorical moderators of the Conscientiousness and medication adherence association. Medication adherence measurement (Q=0.408, df=1, p=0.52), conscientiousness measurement (Q=1.573, df=1, p=0.21), study design (Q=0.15, df=1, p=0.70) and sample type (Q=0.546, df=1, p=0.46) were not significant moderators of the conscientiousness and medication adherence association according to the between-group test of heterogeneity in the random effects model. Age (Q=7.695, df=1, p=0.006) and whether statistical controls were used in the analysis (Q=11.371, df=1, p=0.001) did emerge as statistically significant moderators of the Conscientiousness and medication adherence association. The association was significantly stronger in studies with a mean age less than 50 years old and in studies that did not include adjustments for covariates.

Discussion

This meta-analysis provides four important new findings. First the results confirm that greater conscientiousness is associated with better medication adherence, which gives increased confidence in the validity of early observations

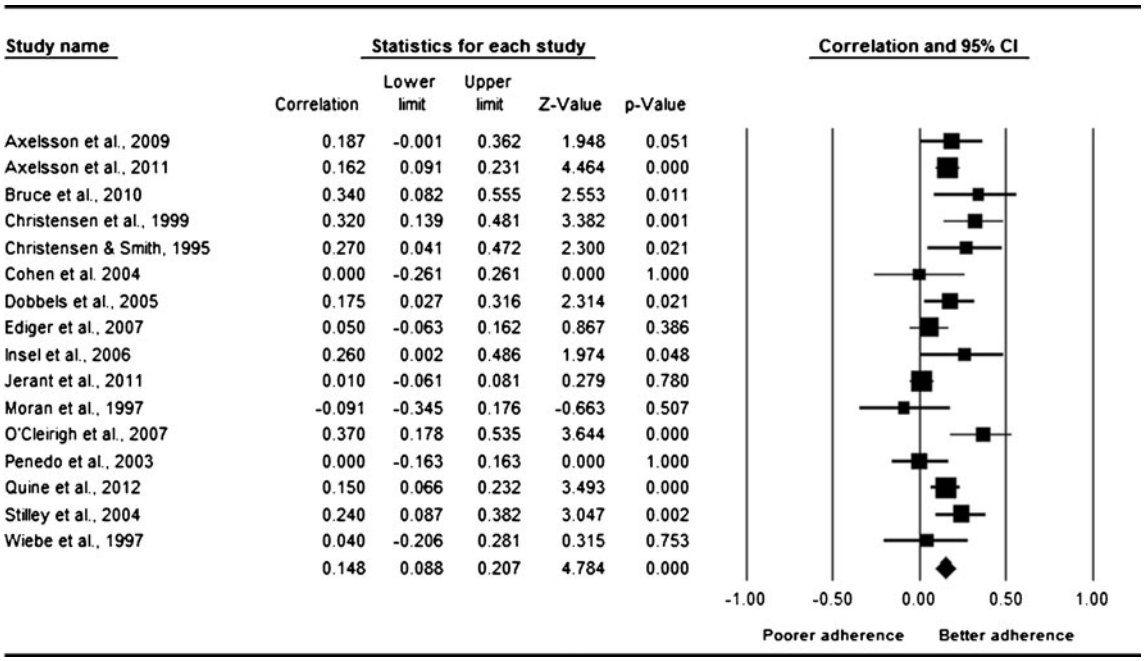

Fig. 1 Forest plot of the observed associations between conscientiousness and medication adherence

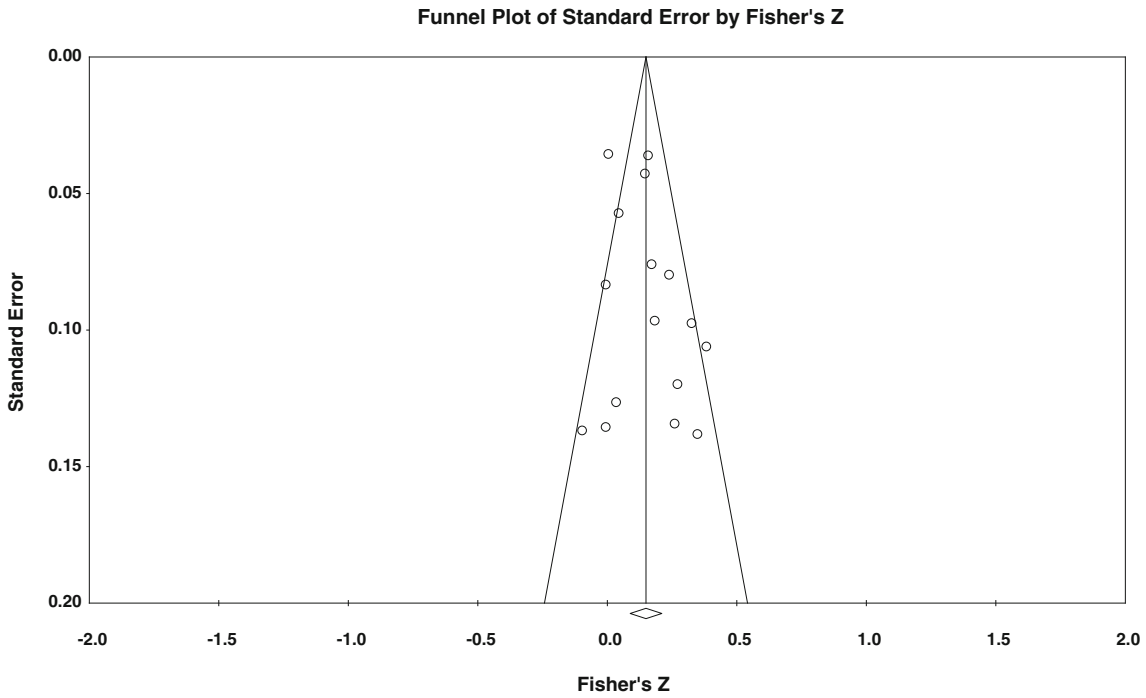

Fig. 2 Funnel plot of the 16 included studies

[20]. Second, the magnitude of this association (r=0.15) is comparable to better established and clinically acknowledged [34] psychological predictors of poor medication adherence such as depression which has been recently estimated as r=−0.16 in a meta-analysis of 31 studies and 18,245 participants in the USA [43]. Third, the moderation analysis revealed that the association between conscientiousness and medication adherence was stronger in younger samples and in analyses where there were no adjustments for covariates. This suggests that conscientiousness may be particularly

Table 2 Summary of potential categorical moderators of the conscientiousness and medication adherence association

Moderator	Number	*k*	*r* (95 % CI)	*Z*	*P* value	FSN	Egger's intercept
Medication adherence measurement							
Self-report only (yes)	2,186	8	0.164 (0.086, 0.240)	4.100	<0.001	98	1.12
Self-report only (no)	1,290	8	0.125 (0.029, 0.218)	2.560	0.010	18	1.51
Conscientiousness measurement							
NEO	2,665	12	0.126 (0.056, 0.195)	3.507	<0.001	84	0.90
Other measure	811	4	0.214 (0.094, 0.327)	3.474	0.001	27	1.65
Study design							
Cross-sectional	1,255	5	0.165 (0.061, 0.266)	3.095	0.002	34	0.30
Prospective	2,221	11	0.140 (0.062, 0.216)	3.528	<0.001	72	1.47
Sample type							
Patient samples	2,547	14	0.158 (0.093, 0.221)	4.736	<0.001	171	0.34
Healthy samples	929	2	0.100 (−0.042, 0.237)	1.383	0.167	–	–
Mean age of sample							
Less than 50 years old	626	7[+]	0.255 (0.166, 0.340)	5.490	<0.001	68	−0.73
Greater than 50 years old	2,524	8	0.098 (0.031, 0.164)	2.865	0.004	31	−0.22
Controls used in analysis							
Yes *r* adjusted	1,130	3	0.015 (−0.068, 0.098)	0.353	0.724	0	−0.63
No *r* unadjusted	2,346	13	0.182 (0.132, 0.232)	6.996	<0.001	213	0.70

[+] One study [77] was excluded as the r estimate from this study included an adjustment for age

important for understanding poor adherence earlier in the lifespan and that there are likely to be a number of important mediators and moderators of this relationship. Fourth, the association does not appear to be an artefact of self-report biases as there was no observed moderating effect for type of measurement used to assess medication adherence.

As conscientiousness has been linked to better survival in observational studies [12, 44–47], better medication adherence may partly explain this association, particularly in patient samples where medication can play an important part in optimising secondary prevention of illness [46]. One recent study provides support for these hypotheses by showing that self-efficacy for medication adherence can account for the association between conscientiousness and perceived health among older adults [48]. This kind of mediation analysis provides information for developing behaviour change techniques to enhance adherence to medications in those with chronic illness, as key modifiable mechanisms are identified [49, 50].

The overall summary effect size observed in this analysis was in the small range according to Cohen's criteria [37]. Therefore, it is important to acknowledge that the amount of variability that it can account for is relatively small at approximately 2 %. This is perhaps not surprising given the complexity of the behaviour of medication taking [2]. It is worth considering that while the effect sizes may be small, the clinical impact may be large if small differences in adherence can result in clinically significant effects. For example, increasing adherence by one anti-hypertensive pill per week for a once a day regimen reduces the hazard of stroke by 8–9 % and death by 7 % [51] and small deviations from the prescribed medication regimen of warfarin, a highly efficacious anticoagulant, can result in immediate and substantial clinical risk to patients prescribed this medication [52]. Medications such as this that carry substantial risk may be less suitable for those who have lower levels of conscientiousness and equally medications that require very high levels of adherence, such as highly active antiretroviral therapies [53], to achieve efficacy may be less effective in those lower in conscientiousness due to poor adherence.

The effect sizes also have to be understood within the wider theoretical framework [9] that predicts that conscientiousness will influence adherence via cognitive processes (e.g. memory) [27] and social cognitive processes (e.g. intentions and self-efficacy) which are known determinants of medication adherence [11]. Thus, the effect sizes reported here are likely to represent either the total or direct effects and there may still be indirect routes via these cognitive and social cognitive processes. Furthermore, the model [9] also indicates that conscientiousness has a direct effect on health behaviour [19]. Thus, the small effect size should not be seen to indicate that there is not a central role for conscientiousness in understanding health outcomes more generally. This meta-analysis reflects the average linear effects that differ between individuals rather than the nonlinear interactions of conscientiousness with other variables within individuals [54].

An important consideration relates to whether conscientiousness (and traits in general) provides useful information to health care professionals. If as detailed above conscientiousness is linked to behaviours that influence both medication adherence and behaviours that can influence the effectiveness of medications, e.g. alcohol consumption, then knowing that someone is low in conscientiousness is important clinically [9], particularly if it provides information on an individual's likelihood of benefiting or being harmed from a treatment, i.e. those low on conscientiousness may take too little or too much of their medication resulting in a lack of treatment benefit or in some instances increased risk of harm [52]. This information can be used to trigger questions about lifestyle and start appropriate interventions. It is possible that some of the shorter indices of conscientiousness [55] can be easily administered as part of a time-constrained clinical interaction, as the number of items included are similar to instruments used to assess depressive symptomatology in clinical practice [56]. However at present there are no defined ways to categorise low versus high conscientiousness. While taxometric analysis of conscientiousness have not been conducted recent narrative reviews suggest that it is likely to be continuous [57], as are other personality traits related to health [58, 59]. Latent profile analyses or ROC curve analyses may be ways forward to identify how levels of a trait (and conscientiousness in particular) are linked to adherence [60]. Therefore, at present for clinicians levels of conscientiousness should be used as an additional piece of information to guide and inform practice, maybe relative to established norms, rather than as a diagnostic [9].

Where patients are identified as lower in conscientiousness certain behaviour change techniques [61] could be used to enhance adherence to medications. For example, recent randomised controlled trials of very simple planning interventions have led to significant improvements in medication adherence among patients with epilepsy and patients following stroke, who were having difficulty with taking their medication as prescribed [62, 63]. There is recent evidence however indicating that there are individual differences in the capacity to make plans, therefore there may be trait level moderators of the effectiveness of some of these interventions approaches [64]. Theoretically, one would expect that certain behaviour change techniques that engage more reflective process might be less effective for those lower in conscientiousness, e.g. goal setting, comparison of outcomes and shaping knowledge [65], as these require capacities that may be, by definition, weaker in this group, e.g. the conscientiousness facets of orderliness, self-control, decisiveness and persistence [13].

Finally, there is a growing theoretical [9, 66] and empirical literature [67, 68] indicating that normal personality traits can change as a function of pharmaceutical [67] and behavioural interventions [68]. As such, clinicians and practitioners should not see traits as fixed but realise that interventions and medications may also influence the trait and as such traits should be measured across the time course of illness and intervention [9].

There are a number of limitations to this analysis which should be acknowledged. First, the available observational data did not allow us to make causal inferences or to examine whether particular facets of conscientiousness [26], e.g. Industriousness and Orderliness, were associated with medication adherence, as the data on these subcomponents was not provided in enough of the reviewed studies. It is possible that medication adherence may be more or less associated with the facets that comprise the higher order personality factor of conscientiousness. Second, in relation to the medication adherence measures we were unable to distinguish between intentional and unintentional non-adherence, as none of the included studies had separate measures. It is increasingly recognised that this is an important distinction to make [69] given the differing role of motivational and volitional processes in each kind of non-adherence [63]. Finally, it has argued theoretically [9] and been demonstrated empirically that the personality [70, 71] of others in one's immediate ongoing social environment, e.g. partner or one's doctor, may have important effects on health and health relevant behaviour. For example, a health protective effect has been observed when one's spouse has higher levels of conscientiousness in a large sample of older adult couples in the USA [70]. None of the studies in the present meta-analysis examined this 'compensatory conscientiousness' phenomenon, which may be linked to better medication adherence, if one person in an ongoing stable relationship directs health related behaviour for both members of a dyad [72]. Future multilevel studies can examine the extent to which dyad-level conscientiousness is critical for good medication adherence and whether medication adherence is best considered a behaviour that is regulated within ongoing social relationship as some recent work has suggested, e.g. patient–informal carer dyads [73].

Conclusions

Conscientiousness accounts for a significant proportion of the variability in the extent to which people adhere to medications. Future studies that identify the modifiable processes that explain this link (e.g. cognitive and social cognitive processes) and the key moderators of these processes may help in the design of interventions to enhance medication adherence.

Conflict of Interest The authors have no conflict of interest to disclose.

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