How to make value based health insurance designs more effective? A systematic review and meta-analysis

Abstract

Value based health insurance designs (VBIDs) are one approach to increase adherence to highly effective medications and simultaneously contain rising health care costs. The objective of this systematic review was to identify both VBID effects on adherence and incentive designs within these programs that were associated with higher effects. Eight economic and medical databases were searched for literature. Random effects meta-analyses and mixed effects meta-regressions were used to synthesize VBID effects on adherence. Thirteen references with evaluation studies, including 12 patient populations with 79 outcomes, were used for primary meta-analyses. For qualitative review and sensitivity analyses, up to 19 references including 20 populations with 119 outcomes were used. Evidence of synthesized effects was good, because only references with low risk of bias were included. VBIDs significantly increased adherence in all indication areas. Highest effects were found in medications indicated in heart diseases (4.05%-points, $p<0.0001$). Each additional year increased effects by 0.15%-points ($p<0.01$). VBIDs with schooling were more effective than without schooling, but the difference was not significant. Effects of VBIDs with full coverage were more than twice as high as effects of VBID without that option (4.52 vs 1.81%-points, $p<0.05$). These findings were robust in most sensitivity analyses. It was concluded that VBID implementation should be encouraged, especially for patients with heart diseases, and that full coverage was associated with higher effects. This review may provide insight for policy makers into how to make VBIDs more effective.

Keywords value based health insurance design, health insurance, cost sharing, adherence, meta-analysis

JEL Classification D81 H75 I13 I12 I18

Introduction

Costs of pharmaceutical products account for a large share of rising health care costs in many European and other high income countries [1]. As a result, private health insurers and social health insurance systems have increased cost sharing for prescription medications to decrease unnecessary health care utilization [2,3]. However, concerns have been raised that the utilization of clinically important, high-value medications is decreased as well. The financial burden of cost sharing could be problematic, especially for the sick and the poor [4,5]. In 2016, about 33% of surveyed respondents in the United States (US) and about 7–18% of respondents in selected European and other high income countries faced financial barriers to health care [6]. Because cost sharing is usually based on costs and not on clinical value, patients may prefer less effective medications with lower cost sharing over indicated but expensive, high-value medications. Non-adherence to high-value medications is problematic because it is considered to be associated with worse health and, therefore, increased health care costs [7].

In 2001, Fendrick et al. [8] proposed a benefit-based copay to simultaneously contain cost and increase adherence. They proposed a benefit-based copay that is based on the clinical value of medications, not on costs. Health insurance designs that use benefit-based copays are called *value based health insurance designs (VBIDs)* [9]. According to the original idea, apart from decreased cost sharing for high-value medications, VBID may also include increased cost sharing for low-value medications. However, to date, most VBIDs only reduced cost sharing for high-value medications [10].

Because of promising results from the first experimental implementations of VBIDs, the number of health plans that offer VBIDs to patients with chronic diseases is increasing. For example, in France and the UK, some long term diseases are exempt from cost sharing [2]. In Germany, patients with chronic diseases usually do not have to pay more than 1% of their income and, in the US, the Patient Protection and Affordable Care Act requires health plans to fully cover certain preventive services [2,11]. To increase patients' understanding of the importance of high-value medications, VBIDs are often implemented in combination with *schooling programs*, such as educational material, nurse counseling, or more complex disease management programs (DMPs).

Previous systematic reviews found that lower cost sharing was able to increase the number of adherent patients without increasing total health care spending [12-14]. Many VBID evaluation studies have reported effects on adherence of patients with different chronic diseases and after different lengths of follow up. Sometimes, the effects were also stratified to different medication classes [15-17]. To date, the evidence related to these outcomes has not been comprehensively synthesized. A comprehensive synthesis would provide better insight not only into whether VBIDs are effective, but where they are most effective and if VBID effects evolve over time.

To answer the question how to make VBIDs more effective, VBID incentive designs that are associated with higher effects need to be identified. This cannot be done by evaluation studies of a single VBID, only by comparison of effects across multiple VBIDs with different designs. It was found in a systematic review that lower cost sharing was associated with higher adherence [12]. However, it was not analyzed whether this finding was statistically significant. An empiric evaluation study of multiple VBIDs found that VBIDs that were more generous did not include a DMP, were offered to high risk patients, and associated with higher adherence [18]. However, because these analyses were based on VBIDs from a single pharmacy benefit manager and not on a

systematic review, the generalizability of these findings is limited. A recent systematic review and meta-analyses found that the risk of non-adherence decreases with full coverage [19]. However, it is unclear whether this decline was significant. Furthermore, this study synthesized the outcomes of non-interventional studies, and it seems as though multiple outcomes from a single population were included without consideration of correlation between these outcomes [20,19]. Therefore, to the knowledge of the author, there is no reliable evidence from meta-analyses about the VBID effect on adherence.

To answer the question how to make VBIDs more effective, a systematic review and meta-analyses were chosen. Specifically, the objective was to identify the VBID effect on adherence and incentive designs within these programs that were associated with higher effects. To follow that objective, the overall effect on adherence and VBID time trend effects was analyzed. This was differentiated between effects on adherence to different medication classes and effects on adherence to medications prescribed for different indication areas. It was further analyzed whether incentives exerted by VBIDs and schooling were associated with higher effects.

Methods

Systematic search and selection process

A systematic literature review was done in accordance with the Cochrane Collaboration recommendations [21]. Eight databases comprising medical, economic, health behavioral, and interdisciplinary research were searched on May 16, 2018: PsycINFO, Medline, EconLit, and Business Source Complete via EBSCOhost; Cochrane Library; ClinicalTrials.gov; Scopus; Web of Science Core Collection. Inclusion criteria were:

1. Empiric interventional evaluation studies of health plans with reduced cost sharing for medications prescribed for chronic diseases (heart diseases, diabetes, hyperlipidemia, hypertension, COPD, asthma). *Cost sharing* must be a percentage of costs or a fixed copay. Caps were excluded because they do not affect patients with low utilization.
2. No study with negative cost sharing was included. *Negative cost sharing* means that patients received a net gain from filling prescriptions, for example because cost sharing was overcompensated by payments for prescription fills [22].
3. Included comparisons are:
    - VBID vs usual medication coverage (VBID vs U)
    - VBID + schooling vs usual medication coverage (VBID + S vs U)
    - VBID + schooling vs usual medication coverage + schooling (VBID + S vs U + S)
4. Adherence must be measured as the percentage of days with prescribed daily dose available (e.g., as proportion of days covered or medication possession ratio). In non-randomized studies, effects on adherence must be given as before–after values in treatment and control groups or measured by a difference in difference (DiD) framework.
5. Quantitative synthesis of reported outcomes with inverse variance method must be possible [23]. Therefore, standard errors of VBID effects on adherence must be reported or possible to calculate.
6. For inclusion into meta-analyses: only references without high risk of bias.

VBID is usually defined as any health insurance design that aims to increase adherence to high-value medications by monetary incentives [8,9]. However, the analyses in the present review were restricted to reduced cost sharing designs because empiric evidence about increased cost sharing for low-value medications was found to be scarce [24,2]. To ensure that reduced cost sharing was associated with clinical value, only VBIDs for medications prescribed for specified chronic diseases were included. Programs with negative cost sharing were excluded because, according to prospect theory, incentives exerted by gains and losses may not be comparable [25]. In order to be able to identify causal VBID effects on adherence, either randomized controlled trials (RCTs) or non-randomized studies that enable a DiD framework were included [26]. To ensure high quality of synthesized evidence, studies with high risk of bias determined by risk of bias assessment were excluded from meta-analyses, but included in qualitative overviews and sensitivity analyses.

The search strategy was built from terms and synonyms for specified chronic diseases and related medications, cost sharing, health plans or prospective and retrospective study designs, and for adherence. The search strategy is presented in Appendix A. It was adjusted slightly for different databases. Given the inclusion criteria and search strategy, two researchers independently selected relevant literature. Discrepancies were solved by discussion.

Data extraction

Basic characteristics of each VBID evaluation, such as its name, the length of follow up, and the index year, were extracted from the literature. The index year is the year of VBID implementation. Data were extracted on the level of each patient population in which the effects of VBID were evaluated because, in this meta-analysis, effects on level of populations, not on level of references, were synthesized (see chapter "Handling multiple outcomes within the same population").

A combination of the name of the VBID evaluation study, and possibly the subgroup and the index year, was used for each distinct population as a population identifier (ID) (e.g., "CHORD 2 ambulatory clinics, 2005"). If the evaluation study or VBID did not have a name, the name of the insurance group or initiator of the program was taken, e.g., "A large employer".

Because VBIDs were often combined with schooling interventions, which are also designed to increase adherence, schooling effects might bias VBID effects. *Schooling effects* were identified if VBID was combined with an existing schooling (S_{old}) or simultaneously implemented with a new schooling program (S_{new}). Because of the DiD framework, independent schooling effects of VBID + S_{new} vs U + S_{new}, VBID + S_{old} vs U + S_{old} , or VBID + S_{old} vs U comparisons are canceled out (Appendix B). However, VBID–schooling interaction effects or long term schooling effects might exist anyway. *No schooling* effects were identified in VBID vs U comparisons.

VBID incentive designs were analyzed in detail: a VBID was defined to include *full coverage* if either full coverage was provided for at least one tier or for all medications. It was also assessed whether schooling was individualized or standardized. *Individualized schooling* was defined as schooling that included at least individualized information or complex disease management, such as nurse counseling. Schooling was classified as *standardized* if the same information was provided to each patient, for example by informational letters, workbooks, or movies.

For quantitative synthesis, VBID effects on adherence percentage-points (%-points) and statistics that are required for meta-analysis were extracted from the literature. If multiple references were published on the same VBID program, only effects of references that contributed additional information to previously published effects were extracted to avoid double counting of effects. Examples are already evaluated VBIDs that are evaluated in a new population or references that contribute a new outcome (e.g., effects on adherence after a longer follow up).

In case of missing information, corresponding authors of primary studies were contacted. Results after match or after further adjustments were preferred to descriptive results. Correctness of data extraction was revised by a research assistant.

Risk of bias

Risk of bias was assessed by the risk of bias tool developed by the Cochrane Review group "Effective Practice and Organization of Care" (EPOC). This tool requires separate assessments of risk of bias in the nine domains. The tool is recommended for randomized and non-randomized trials and controlled before–after studies [21]. Risk assessment was done on outcome level if possible and on level of reference otherwise. Risk of bias was rated "high" if the evaluation design points to potential problems in respective domains and "low" if those problems could be ruled out. Risk of bias was rated "unsure" if the information given in the reference was not sufficient to identify potential problems. Details about decision rules and risk domains are published elsewhere [21].

Summary effect measure and standard errors

The VBID effect on adherence %-points was used as a *summary effect measure*. *Adherence* was defined as the percentage of days with prescribed daily dose availability. For each effect extracted from primary studies, it was determined to which medicine or indication it related and whether it was assessed up to 1, 2, or 3 years after the VBID index date. For non-randomized studies, effects determined by a DiD framework were used. If these effects were not given in the primary literature, they were calculated based on the given data. In RCTs, differences in adherence between treatment and control group after VBID implementation without pre-index values was also allowed, because effective randomization ensures similar baseline characteristics between groups [27].

Standard errors of effects were extracted from primary references. If standard errors were not reported, they were calculated with decreasing priority with: (i) 95% confidence intervals; (ii) standard deviations and population sizes; (iii) p-values and population sizes. However, to verify the results, all methods were tested. It was found that methods (i) to (iii) identified very similar standard errors. If exact p-values were not given, the level of significance of significant effects was set to be equal to the p-value. This is a conservative approach, because it overestimates the p-value of significant effects and large p-values imply larger standard errors. Utilized methods for the calculation of standard errors are well known standard statistical methods [28,29]. They are, for example, implemented in Review Manager 5.3.

Handling multiple outcomes

Meta-analyses of effects require that effects of distinct and independent study populations are synthesized [30]. To adequately control for correlations between multiple outcomes within the same population and to avoid

double counting of effects, populations rather than single references were synthesized. Before entering effects into meta-analyses, correlated outcomes within the same population were combined by a method that considers correlations and is published elsewhere [28]. Because good evidence about correlations between adherence outcomes was not found in the literature and complete dependence or independence was considered to be unlikely, a conservative assumption of a fairly high correlation (r = 0.8) was chosen.

Combination of correlated effects was done for each year after the index year on three *levels of aggregation*: *medication class*, *indication area*, and *population level*. For example, VBID effects on adherence to all oral antidiabetics are combined to the medication class "oral antidiabetics", and all effects on insulins are combined to the medication class "insulin". The medication classes "insulin" and "oral antidiabetics" are combined to indication area "diabetes". All identified VBID effects were finally aggregated to a population level. Detailed definitions for levels of aggregation are given in Appendix C.

Meta-analyses

A meta-analysis on continuous data with generic inverse variance method was used to analyze the association between incentive designs and strength of VBID effects. This was done by following subgroup analyses of populations that participated in VBIDs with different incentive designs: VBIDs with vs without schooling, with vs without individualized schooling, and populations with full vs partial medication coverage. VBID effects on population level that were evaluated at the end of follow up were included in this analysis.

Because of the heterogeneity of VBID characteristics, incentives, and other confounding, population-specific effects, huge heterogeneity of VBID effects must be expected between patient populations. To account for that heterogeneity, random effect models rather than fixed effect models are chosen. While the fixed effect approach assumes that the between-population variance of effects is zero, the random effects approach controls for that heterogeneity by assuming that the effect estimate varies randomly between populations. Heterogeneity of effects was primarily assessed by between-population variance of effects τ^2, which was estimated by the DerSimonian–Laird method [31,23]. A 5% level of significance was chosen for calculation of standard errors in all analyses.

To estimate time trend-adjusted VBID effects on adherence, three meta-regressions were used. Time trends were estimated as the years elapsed since the VBID index date. A fixed time trend effect was used in all models to adjust the VBID effect. All models used a random, population-specific effect to control for unobserved heterogeneity between populations and to control for correlated effects in populations with multiple outcomes [32]. In the first model, the mean VBID effect was estimated. All VBID effects at the population level were included in this analysis. Because some populations were evaluated at different points after the index year, multiple outcomes may exist per population. The same applies to the second (and third) model, where VBID effects on the level of different indication areas (and medication classes) were estimated accordingly. As before, multiple outcomes per population may occur if evaluations are done after multiple observation periods.

In the first model, the time trend effect might be biased by indication area. Because not all references reported VBID effects on medication class level, the third model does not include all populations identified by this review. Therefore, the second model was used to interpret VBID time trend effects.

Sensitivity analyses

To verify the robustness of VBID effects, sensitivity analyses were done. Meta-analyses were rerun with varying assumptions of correlation between adherence outcomes within the same population: perfect independence, medium correlation, and perfect dependence (r = 0, 0.5, 1). In further sensitivity analyses, influence analyses were conducted: first, an outlier was omitted from meta-analyses. Second, all references, including those with high risk of bias, were included.

Publication bias

A contour enhanced funnel plot was used to interpret small study effects in meta-analysis across all included populations. Compared to usual funnel plots, contour enhanced funnel plots facilitate the distinction of small study effects that are caused by publication bias from other sources of asymmetry by visualizing areas of statistical significance [23,33]. Although other causes or pure coincidence could result in small study effects, contour enhanced funnel plots are commonly used as an indicator of publication bias [33,34]. Under the assumption that asymmetry of VBID effects was caused by publication bias, trim and fill methods are used to estimate missing studies [33].

All statistical analyses are done with R 3.4.3. Graphics are done with R 3.4.3, OpenOffice 4.1.5, and Inkscape 0.92.

Results

Selection process

A total of 3798 records were found by database searches (Fig. 1). Another 35 abstracts were found through other sources. After excluding duplicates, 2419 abstracts were screened. Finally, after applying inclusion criteria, 19 references about 20 populations were included in this review and in sensitivity analyses. Thirteen references with 12 populations were included in primary meta-analyses.

++++++++ **Fig.1** Flow chart ++++++++++++++++++++

Summary of included studies

An overview of all populations and interventions is given in Table 1. Two RCTs [15,35], including one cluster RCT and one interrupted time series [36], are identified. All other references include retrospective controlled before–after analyses on claims data [37,16,38-47,17,48-50]. Of retrospective evaluation studies, one natural experiment was identified with reduced copay because of patent expiration [49]. The VBIDs were implemented between 2005 and 2014 in the US. Maximum follow up ranged between 9 and 36 months. The VBID programs lowered copay in the indication areas heart diseases, asthma, and diabetes. Outcomes are reported on the level of these indications or on the level of medications prescribed for them. Full coverage for at least one tier was offered to 15 populations. In five populations, cost sharing was lowered but not waived. In 16 populations, schooling interventions were implemented before or in combination with the VBID. In four populations, VBID alone was compared to usual health care coverage. Individualized schooling interventions were implemented in 13 and standardized schooling in seven populations.

++++++++++++++ **Table 1** Included references and populations ++++++++++++++++++

Risk of bias

An overview of results from the risk bias assessment is presented in Appendix D. Risk of bias from inappropriate random sequence generation and allocation concealment was low in RCTs. Because retrospective controlled before–after studies are not randomized, all other references have a high risk of bias in these domains [21]. In all retrospective studies, baseline differences could be adequately controlled by DiD frameworks, confounder adjusted estimations, and matching techniques. Therefore, risk of bias from dissimilar outcome measurements was low. Risk from dissimilar baseline characteristics was also low in five cases (similar characteristics) and high in 10 references (dissimilar characteristics). In five other references, baseline characteristics were reported, but significance of differences was not analyzed (unclear risk). All RCTs and Clark et al. [38] had complete outcome data or none or only a few participants who were lost to follow up (low risk of bias from incomplete outcome data). In all other references, the proportion of missing data or the number of participants lost during follow up was not reported (unclear risk). Generally, risk of bias from knowledge of the allocated intervention can be rated low, because the outcome was based on claims data, which are objective [21]. In two references, the health plans of enrollees were not known to the investigator. Therefore, unobserved implementation of changes in cost sharing could be possible and risk of contamination bias was high. In other references, risk of contamination bias was low. In the analyses of Reed et al. [48], treatment and control group changed to a high deductible plan, in the VBID analyzed by Volpp et al. [35], cost sharing was reduced through payments for prescription fills, and in Sedjo, Cox [49], the analysis is based on a natural experiment of patent expiration, which could limit the generalizability of findings. Therefore, risk from other causes was rated high. In three references on five populations, the control group was constructed from patients who declined program participation [38,47,50]. Because of this self-selection, risk of bias from other causes was also high in these references.

References with high risk of bias were excluded from primary meta-analyses, with some exceptions: references with high risk of biases because of non-randomization (domains “random sequence generation” and “allocation concealment”) were not excluded because this meta-analysis should not be restricted to RCTs. Aside from that, potential differences in baseline characteristics are controlled by DiD frameworks and were therefore accepted. Because risk of attrition bias could be an issue in almost all references, it was also accepted. Finally, six references with eight populations were excluded from primary meta-analyses.

The VBID effect on adherence

Synthesized VBID effects on adherence at the population level are depicted in Fig. 2. Significant and positive effects are found in all populations. The unadjusted effect in 12 independent populations was 3.76 %-points ($p < 0.01$). The highest effect was found in “A large employer, 2010”, where adherence increased by 14.10 %-points. In this population, a VBID with full coverage for generic medications and reduced copay for preferred brands with min/max thresholds for copays and 50% coinsurance for non-preferred medications was evaluated. These monetary incentives were combined with a health and disease coaching program (see Appendix E for details on intervention designs).

++++++++++ **Fig.2** Forest plot-VBID effects on adherence in included populations ++++++++++

The time trend-adjusted VBID effect on adherence was 3.18 %-points ($p < 0.01$) (Table 2). In adjusted analyses, K = 19 effects were synthesized. These effects were contributed by all 12 populations, which are included in

primary meta-analyses. Of these, five populations contributed multiple outcomes after different lengths of follow up. This explains the number of synthesized effects. In the meta-regression model 2, on the level of indication areas, VBID effects are significant in each indication (29 effects contributed by all included populations). Highest effects are found for medicines that are indicated in heart diseases (4.05 %-points). Each additional year significantly increased this effect by 0.15 %-points ($p<0.01$). In model 3, the meta-regression on medication class level, the VBID effect on adherence was significant in three of seven medication classes. A total of 31 effects contributed by 10 populations could be included in this model. Highest VBID effects are found on adherence to lipid-lowering medication (4.66 %-points, $p < 0.01$) and to oral antidiabetics (4.60 %-points, $p < 0.01$).

+++++ **Table 2** Adjusted VBID effects on adherence ++++++++++++

Results from all sensitivity analyses are given in Appendix F. In all influential analyses, VBID effects remained significant and time trends were robust. When the outlier was excluded, VBID effects remained most effective in heart diseases, but all effect sizes decreased. VBID effects were robust to inclusion of effects with high risk of bias and to varying assumptions of correlation.

VBID incentive designs

VBIDs that were combined with an existing or new schooling intervention were more effective than VBIDs without schooling (3.95 vs 2.89 %-points), but the difference was not significant (Table 3). VBID effects on adherence did not differ between VBIDs with individualized schooling programs and VBIDs with standardized or no schooling. A large difference was found between VBIDs that offered full coverage options and VBIDs with only partial coverage. Effects of VBIDs with full coverage were more than twice as high as effects of VBIDs without that option (4.52 vs 1.81 %-points, $p<0.05$).

+++++ **Table 3** VBID effects on adherence in different VBID incentive designs ++++++++++

Significance of differences between populations with different VBID incentive designs was robust to varying assumptions of correlation (Appendix F). In influential analyses, exclusion of the outlier "A large employer, 2010" led to insignificant differences between effects of VBIDs with and without full coverage. However, significant differences between groups remained when all references identified by this review, including high risk of bias effects, were synthesized. In contrast to primary analyses, inclusion of all references was associated with significantly higher effects in VBIDs that were combined with individualized schooling interventions compared to VBIDs with standardized or no schooling (4.57 vs 2.46 %-points, $p<0.05$). Furthermore, the p-value of the schooling effect improved (from $p = 0.90$ to $p = 0.08$).

Publication bias

The contour enhanced funnel plot shows that effects scatter symmetrically around the random effect estimate, which is represented by the dotted line (Fig. 3). Although all effects were significant, with the trim and fill method, no potentially unpublished effects were estimated into the white area of insignificance. Therefore, no small study effect could be detected. However, as shown in the selection process, three references could not be included because of missing information to calculate standard errors (Fig. 1).

+++++ **Fig.3** Contour enhanced funnel plot -VBID effects on adherence in included populations ++++++++++

Discussion

The objective of this systematic review was to identify both VBID effects on adherence and incentive designs within these programs that were associated with higher effects. The findings of this study may provide managerial implications for the implementation of highly effective VBIDs. In meta-analyses, 12 distinct populations were included in primary meta-analyses, and up to 20 populations were synthesized in sensitivity analyses.

The VBID effect on adherence

It was found that, across all indication areas, VBIDs significantly increased adherence by 3.18 %-points. Stratified to indication areas, VBIDs significantly increased adherence to medications that are indicated in asthma, diabetes, and heart diseases, but this was highest in heart diseases (4.05%-points, $p<0.0001$). Although these findings were robust to sensitivity analyses, the effect size decreased when the largest outlier was excluded.

VBID effects on adherence differed qualitatively by indication and medication class. There are several possible explanations for this observation. First, baseline adherence in some studies differed between medication classes, which might have an impact on achievable effects [46,50,38]. Second, side effects are dependent on medication class, and side effects have been shown to be a major driver of adherence [51,52].

Each additional year after VBID implementation increased effects in indication areas by 0.15 %-points ($p<0.01$). Only evaluation studies up to 3 years could be identified. Therefore, the time trend might not be generalizable to longer periods. Furthermore, because of unclear attrition bias in most studies, non-adherent patients might have dropped out during follow up. However, the time trend effect was particularly robust in sensitivity analyses with respect to both significance and effect size.

To the knowledge of the author, the present review is the first study that comprehensively synthesizes VBID effects in stratified analyses and also analyzes time trends.

VBID incentive designs

In the present review, it was not possible to quantify the size of monetary incentives because cost sharing structures of the control group or at baseline were mostly not reported. However, it was found that effects on adherence in VBIDs with full coverage were more than twice as high as in VBIDs without that option. This finding was robust to the inclusion of references with high risk of bias, but not to the exclusion of an outlier [16]. The VBID incentive design of that outlier combines all incentive designs that can be expected to be most effective. Therefore, the extraordinary effects might be driven by incentives and not by unobserved confounders. Although subgroup differences were only able to identify correlations, not causality, this is the first systematic review and meta-analyses that analyzed the significance of differences in VBID effects on adherence between different monetary incentive designs.

In populations where VBIDs were combined with schooling interventions, effects on adherence were higher than in populations with other VBIDs, but differences were not significant. Differences between VBIDs with individualized schooling and other VBID designs could not be shown. Although, to the knowledge of the author, the VBID effect of schooling has not been analyzed previously, other studies confirmed the effectiveness of

schooling and similar interventions per se [53,54]. Furthermore, the number of effects that could be used for subgroup analyses of VBID incentive designs was only 12. Of these, in two populations, VBID alone and, in one population, VBID with standardized schooling was evaluated. As the number of included populations increased in influential analyses to 20 populations, the p-value improved. Therefore, this review might simply be underpowered to identify the true schooling effect. Therefore, further VBID evaluation studies are needed to increase the power to analyze schooling effects within VBIDs by meta-analyses in detail.

Limitations

There are several potential limitations to discuss. First, unpublished, insignificant, or negative effects of VBIDs could cause publication bias. Furthermore, three references needed to be excluded because standard errors could not be calculated. However, by the trim and fill method, missing populations could not be estimated and, therefore, no small study effects could be identified.

Second, most subgroup meta-analyses had high heterogeneity between population effects. Heterogeneity might arise from differences between populations in terms of educational background, comorbidities, and other demographic characteristics that are associated with adherence [51], but also from varying study quality or intervention designs. Therefore, a random effects model that adjusted for between-population variance was chosen. Furthermore, meta-regressions were used to control for unobserved population-specific heterogeneity. However, it could not be ruled out that this heterogeneity caused selection bias in subgroup analyses, especially in unadjusted analyses.

Third, meta-analyses were done on continuous data, which assume normally distributed effects [23]. Because the range of possible effects is actually limited, the assumption of normality was violated. However, VBID effects randomly scattered around the effect estimate, did not exceed 15%-points, and the outlier was analyzed in detail. Therefore, the assumption of approximate normality is considered to be reasonable.

Lastly, the generalizability of synthesized effects found is limited because only evaluation periods up to 3 years could be identified, and results are restricted to medications for chronic heart diseases, diabetes, and asthma. Furthermore, only studies from the US were identified, which makes generalization to other countries difficult. Although effects might be smaller in health systems with lower cost sharing, a huge survey of the Commonwealth Fund has shown that individuals in other countries also face financial barriers to adherence and health care [6]. On the other hand, given published evidence, this meta-analysis provides the best evidence available for generalization of VBID effects, as it is the first systematic review and meta-analysis to analyze VBID incentive designs on the basis of high quality research.

Conclusions

The findings of this systematic review and meta-analysis encourage the use of VBIDs as an effective tool to increase medication adherence in health insured patients with asthma, diabetes, and especially heart diseases. It was found that effects increased further with time elapsed since VBID implementation and with full coverage. Further VBID evaluation studies are necessary to thoroughly evaluate the causal effects of VBID incentive designs and especially of VBIDs with schooling. The effect of increased cost sharing in VBIDs was not analyzed in this review and may be the subject of further research. Being the first systematic review and meta-analysis on

the effectiveness of VBID incentive designs, the present study may provide valuable guidance for policy makers on how to make VBIDs more effective.

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Conflict of interests

The author declares no conflict of interest.

Note:

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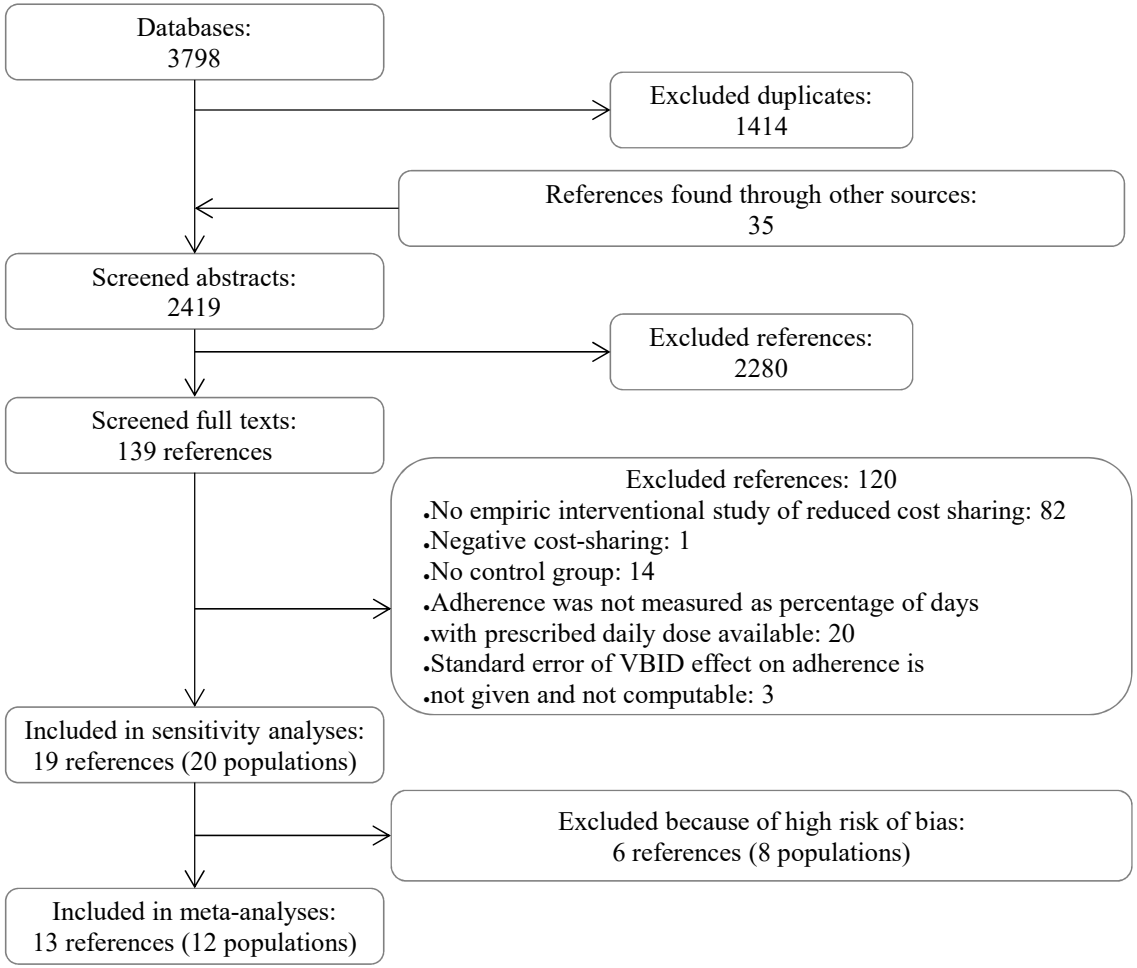
554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2419
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2280
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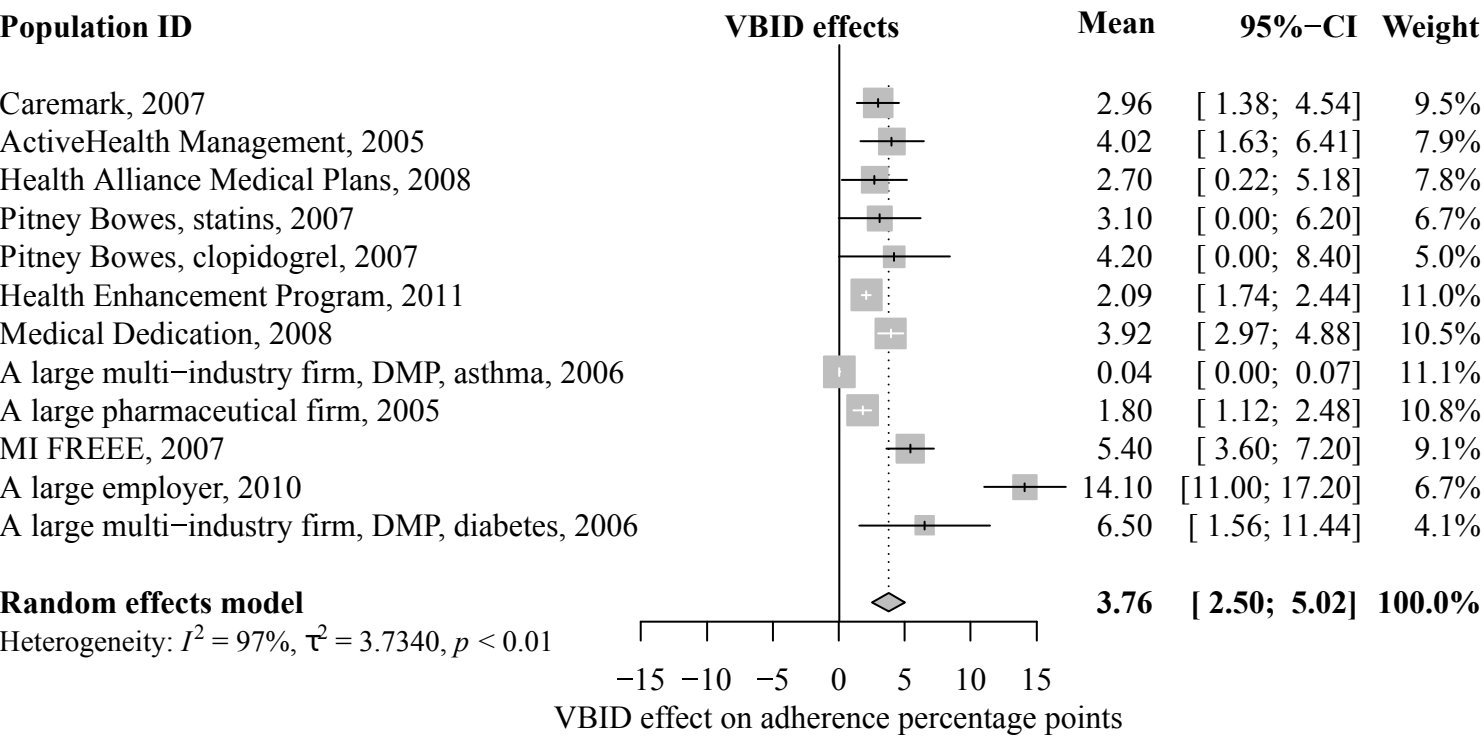
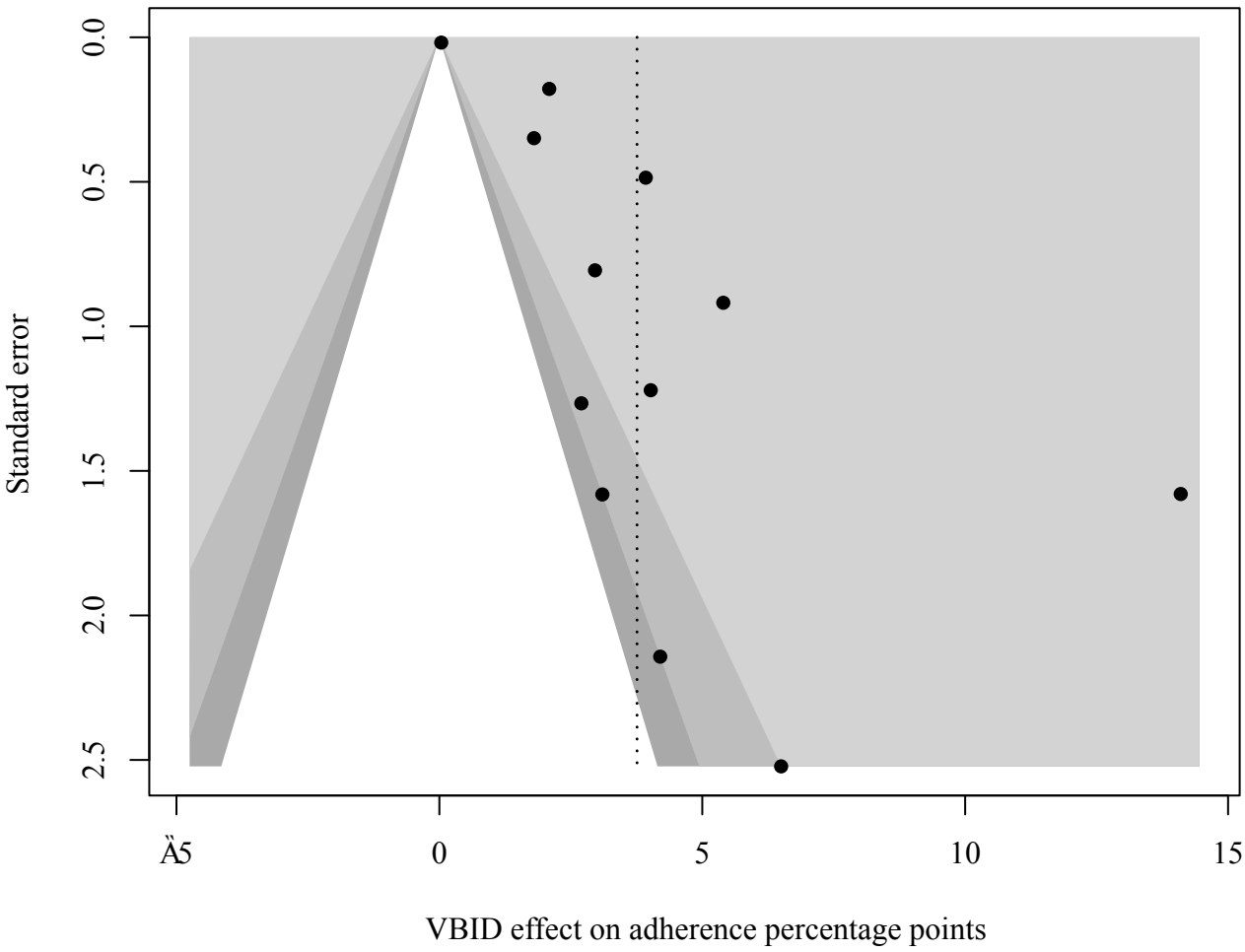
139 references
Excluded references: 120
•No empiric interventional study of reduced cost sharing: 82
•Negative cost-sharing: 1
•No control group: 14
•Adherence was not measured as percentage of days
•with prescribed daily dose available: 20
•Standard error of VBID effect on adherence is
•not given and not computable: 3
Included in sensitivity analyses:
19 references (20 populations)
Excluded because of high risk of bias:
6 references (8 populations)
Included in meta-analyses:
13 references (12 populations)


Population ID
VBID effects
Mean
95%−CI
Weight
Caremark, 2007
2.96
[1.38; 4.54]
9.5%
ActiveHealth Management, 2005
4.02
[1.63; 6.41]
7.9%
Health Alliance Medical Plans, 2008
2.70
[0.22; 5.18]
7.8%
Pitney Bowes, statins, 2007
3.10
[0.00; 6.20]
6.7%
Pitney Bowes, clopidogrel, 2007
4.20
[0.00; 8.40]
5.0%
Health Enhancement Program, 2011
2.09
[1.74; 2.44]
11.0%
Medical Dedication, 2008
3.92
[2.97; 4.88]
10.5%
A large multi−industry firm, DMP, asthma, 2006
0.04
[0.00; 0.07]
11.1%
A large pharmaceutical firm, 2005
1.80
[1.12; 2.48]
10.8%
MI FREEE, 2007
5.40
[3.60; 7.20]
9.1%
A large employer, 2010
14.10
[11.00; 17.20]
6.7%
A large multi−industry firm, DMP, diabetes, 2006
6.50
[1.56; 11.44]
4.1%
Random effects model
3.76
[2.50; 5.02]
100.0%
Heterogeneity: I^2 = 97%, τ^2 = 3.7340, p < 0.01
−15 −10 −5 0 5 10 15
VBID effect on adherence percentage points



Levels of significance

- 0.1 > p > 0.05
- 0.05 > p > 0.01
- < 0.01

Objects

- Population IDs
- Synthesized effect from random effects meta-analysis

Note: No unpublished effects are estimated by the trim and fill method. Synthesized effects from included populations scatter randomly around the pooled effect that was estimated by random effects meta-analysis.

Tables

Table of contents

Table 1 Included references and populations

Population ID[a]	Author, year, Cit. No.	Study design			VBID participants	VBID effects on adherence was analyzed for:	Schooling interventions		Full coverage option	High risk of bias (only included in sensitivity analyses)
		FU[b]	Comparison	Self-selected CG[c]			Schooling effect[d]	Individualized		
Randomized controlled trial										
MI FREEE, 2007[e]	Choudhry, Avorn, 2011, [1]	36	VBID + S_{new} vs U + S_{new}	No	Trial participants got benefits through Aetna, have been hospitalized because of myocardial infarction, not enrolled in health saving accounts and were <65 years of age	• ACEi or ARB • BB • Statin	Yes	No	Yes	
CHORD, 2 ambulatory clinics, 2005	Volpp, Troxel, 2015, [2]	12	VBID + S_{new} vs U + S_{new}	No	Patients of two ambulatory clinics, >21 years of age and no diseases with significantly shortened life expectancy	• Antihypertensives	Yes	No	Yes	X
Interrupted time series										
Pitney Bowes, statins, 2007	Choudhry, Fischer, 2010, [3]	12	VBID + S_{old} vs U	No	Plan participants	• Clopidogrel	Yes	Yes	Yes	
Pitney Bowes, clopidogrel, 2007		12	VBID + S_{old} vs U	No	Plan participants	• Statin	Yes	Yes	Yes	
Retrospective controlled before-after study										
Caremark, 2007	Chang, Liberman, 2010, [4]	12	VBID vs U	No	Commercially insured plan participants of three CSV Caremark clients	• Insulin • Oral antidiabetics	No	/	Yes	
ActiveHealth Management, 2005	Chernew, Shah, 2008, [5]	12	VBID + S_{old} vs U + S_{old}	No	Beneficiaries of a large employer sponsored health plan	• ACEi, ARBs • BB • Diabetes drugs • Statins • Inhaled steroids	Yes	Yes	Yes	
ZCP, 2010	Clark, DuChane, 2014, [6]	18	VBID + S_{new} vs U	Yes	Beneficiaries of a large employer sponsored health plan	• Antidiabetics • Lipid-lowering drugs	Yes	Yes	Yes	X

Population ID[a]	Author, year, Cit. No.	Study design			VBID participants	VBID effects on adherence was analyzed for:	Schooling interventions		Full coverage option	High risk of bias (only included in sensitivity analyses)
		FU[b]	Comparison	Self-selected CG[c]			Schooling effect[d]	Individualized		
Medical Dedication, 2008 [f]	Farley, Wansink, 2012, [7]	24	VBID + S_{old} vs U + S_{old}	No	State employees and dependents, >18 years of age, ensured by BlueCross Blue Shield of North Carolina	• ACEi • ARBs • BB • Metformin • CCBs • CAIs • Statins • Thiazides	Yes	Yes	Yes	
	Maciejewski, Farley, 2010, [8]	12			Plan participants	• Metformin • Diuretics • ACEi • BB • Statins • CCB				
	Maciejewski, Wansink, 2014, [9]	24			Plan participants	• Antihypertensives				
Health Alliance Medical Plans, 2008	Frank, Fendrick, 2012, [10]	12	VBID vs U	No	Beneficiaries 24 employer sponsored plans	• Statins	No	/	No	
A large multi-industry firm, DMP, diabetes, 2006	Gibson, Mahoney, 2011, [11]	36	VBID + S_{new} vs U + S_{new}	No	Beneficiaries of a large employer sponsored health plan	• Insulin • Oral antidiabetics	Yes	Yes	No	
A large multi-industry firm, DMP, asthma, 2006	Mahoney, Lucas, 2013, [12]	36	VBID + S_{new} vs U + S_{new}	No	Beneficiaries of a large employer sponsored health plan	• Asthma medication (controller and reliever)	Yes	Yes	No	
A large pharmaceutical firm, 2005	Gibson, Wang, 2011, [13]	36	VBID + S_{new} vs U	No	Participants of selected plans insured by their employer-sponsored health plan (a large pharmaceutical firm)	• Asthma medication • Diabetes medication • Cardiovascular medication	Yes	Yes	No	
Health Enhancement Program, 2011	Hirth, Cliff, 2016, [14]	24	VBID + S_{new} vs U	No	Beneficiaries of employer sponsored health plan (State of Connecticut)	• Metformin • BB • Loop diuretics • Inhaled corticosteroids • Thiazides • ACEi • ARB • Statins	Yes	Yes	Yes	

Population ID[a]	Author, year, Cit. No.	Study design			VBID participants	VBID effects on adherence was analyzed for:	Schooling interventions		Full coverage option	High risk of bias (only included in sensitivity analyses)
		FU[b]	Comparison	Self-selected CG[c]			Schooling effect[d]	Individualized		
Nurse Counseling, 2008	Kim, Loucks, 2011, [15]	12	VBID + S_{new} vs U	yes	Beneficiaries of an employer sponsored health plan (a large retail employer)	• Oral antidiabetics • Insulin • ACEi, ARB • BB • Statins • Inhaled corticosteroid	Yes	Yes	Yes	X
Health Educational Mailings, 2008		12	VBID + S_{new} vs U	yes	Beneficiaries of an employer sponsored health plan (a large retail employer)	• Oral antidiabetics • Insulin • ACEi, ARB • BB • Statins • Inhaled corticosteroid	Yes	No	Yes	X
A large employer, 2010	Musich, Wang, 2015, [16]	36	VBID + S_{new} vs U + S_{new}	No	Employees and spouses, enrolled in lifestyle management program of a large employer sponsored health plan	• Medicines for diabetes • Medicines for hypertension	Yes	Yes	Yes	
Kaiser Permanente of Northern California, 2014	Reed, Warton, 2017, [17]	12	VBID vs U	No	Beneficiaries of employer sponsored health plans	• Selected drugs used for chronic diseases	No	/	Yes	X
Zocor's patent expiration, 2006	Sedjo, Cox, 2008, [18]	8,9	VBID vs U	Yes	Beneficiaries of 700 plan sponsors with employer sponsored benefits	• Statins	No	/	No	X
CPCP DCP, 2008	Wertz, Hou, 2012, [19]	12	VBID + S_{new} vs U	Yes	Beneficiaries (>18 years) of employer sponsored health plans (City of Cincinnati and Kroger Co.)	• Antihypertensives • Antidiabetics (excluding insulin) • Statins • Lipid-lowering drugs	Yes	Yes	Yes	X
CPCP HHCP, 2008		12	VBID + S_{new} vs U	Yes	Beneficiaries (>18 years) of employer sponsored health plans (City of Cincinnati and Kroger Co.)	• Antihypertensives • Antidiabetics (excluding insulin) • Statins • Lipid-lowering drugs	Yes	Yes	Yes	X

[a] Name of VBID or provider, population, year of VBID implementation
[b] Follow up = study period in months
[c] Applies only to VBID +S vs U comparisons. Self-selection to control group was observed if the control group declined VBID+S participation.
[d] A schooling effect was identified if a VBID was combined with a newly implemented or already existing schooling intervention.
[e] Cluster randomized trial
[f] Redundant subgroups are excluded from all meta-analyses
ACEi = ACE inhibitor, ARB = angiotensin-receptor blocker, BB = beta-blocker, CAI = cholesterol absorbing inhibitor, CCB = calcium channel blockers, CG = control group, Cit. No. = citation number, CPCP = Cincinnati pharmacy coaching program, DCP = diabetes coaching program, DMP = disease management program, FU = follow up, HHCP = healthy heart coaching program, MTM = medication therapy management, S_{new} = newly implemented schooling intervention, S_{old} = existing schooling intervention, U = usual health insurance, VBID = value based health insurance design, ZCP = zero copay program.

Table 1 Included references and populations

Table 2 Adjusted VBID effects on adherence

Meta-regression models	VBID effect [a]	p-value	95% CI
Model 1: population level [b], K = 19			
Mean VBID effect	3.18**	0.0036	[1.04; 5.32]
Model 2: indication area [c], K = 29			
Time trend effect per year	0.15**	0.0029	[0.05; 0.25]
Asthma	3.16**	0.0017	[1.18; 5.14]
Diabetes	2.92**	0.0038	[0.94; 4.89]
Heart diseases	4.05***	<0.0001	[2.07; 6.02]
Model 3: medication class [d], K = 31,			
Anticoagulants	4.02	0.4022	[-5.38; 13.41]
Antihypertensive	2.67	0.0843	[-0.36; 5.69]
Asthma controller	3.55*	0.0240	[0.47; 6.63]
Asthma reliever	-0.52	0.9048	[-9.02; 7.98]
Insulin	3.10	0.0909	[-0.49; 6.70]
Lipid-lowering medication	4.66**	0.0027	[1.62; 7.70]
Oral antidiabetics	4.60**	0.0034	[1.53; 7.68]

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05

[a] VBID effect on adherence percentage points

[b] Overall VBID effect on adherence across all indications and VBID programs, adjusted by time trend effects and random population effects.

[c] VBID time trend effect on adherence per year and mean VBID effect on adherence to drugs prescribed for different indications, adjusted by random population effects.

[d] VBID effect on adherence to different drugs, adjusted by time trend effects and random population effects.

CI = confidence interval, K = number of effects included, VBID = value based health insurance design

Table 2 Adjusted VBID effects on adherence

Table 3 VBID effects on adherence in different VBID incentive designs

Subgroup analyses	K	VBID effect [a]	95% CI, p-value	τ^2
VBID effect on adherence (not adjusted)	12	3.76	[2.50; 5.02]	3.73
Any schooling effect [b]				
Yes	10	3.95	[2.56; 5.34]	3.74
No	2	2.89	[1.55; 4.22]	0
Q-test for subgroup differences			p = 0.2781	
Individualization of schooling [c]				
Yes	9	3.74	[2.31; 5.17]	3.48
No	3	3.75	[2.02; 5.48]	1.36
Q-test for subgroup differences			p = 0.9909	
Full coverage				
Yes	8	4.52	[2.85; 6.18]	4.67
No	4	1.81	[0.08; 3.54]	1.92
Q-Test for subgroup differences			p = 0.0272	

[a] VBID effect on adherence percentage points
[b] VBID was combined with a newly implemented or already existing schooling intervention.
[c] Individualized schooling = the program included at least individualized information or complex disease management; no individualized schooling: standardized schooling or no schooling is combined with VBID.
CI = confidence interval, K = number of effects included, VBID = value based health insurance design

Table 3 Subgroup differences between VBID designs

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How to make value based health insurance designs more effective? A systematic review and meta-analysis

Appendices

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How to make value based health insurance designs more effective? A systematic review and meta-analysis

Appendices

Appendix A: Search strategy

Note: This search strategy was used for EBSCOhost. Adjusted searches are used in other databases.

TX ((heart OR cardiac) AND (artery OR vascular* OR artherothrombo* OR ischemic OR failure) OR coronary OR cardiovascular OR vascular OR stroke OR “myocardial infarction” OR myocardialinfarction OR MI OR “heart attack” OR hypert* OR (atheroscler* AND (heart OR coronary OR cardiac)) OR "blood pressure" OR “angina pectoris” OR hyperlipidemia OR antilipid* OR antihyperlipidem* OR hyperlipidem* OR “lipid lowering” OR (cholesterol AND lowering) OR hypert* OR antihypert* OR anticoagulant* OR anticoagulant OR “beta blocker” OR beta-blockers OR ACE OR ACEs OR “angiotensin converting” OR ARB OR ARBs OR “angiotensin receptor” OR statin OR statins OR “calcium channel” OR CCB OR CCBs OR clopidogrel OR diab* OR antidiab* OR COPD OR "chronic obstructive pulmonary disease" OR asthma)

AND AB (“cost sharing” OR deductible OR copay* OR co-pay* OR coinsur* OR co-insur* OR waive* OR "full coverage” OR "out of pocket" OR out-of-pocket OR oop OR cap OR caps OR "reference pricing" OR VBID OR “value based” OR "benefit based" OR "evidence based" OR V-BID OR "financial incentive" OR "financial benefit")

AND TX (insur* OR employer OR firm OR “health plan” OR “health plans” OR (health AND insur*) OR ((claim OR claims OR administrative) AND (data OR database)) OR RCT OR before-after OR pre-post OR “interrupted time series” OR ((intervention OR controlled) AND (trial OR program OR “insurance design”)))

AND AB (*adhere OR *adherence OR *persist OR *persistence OR *comply OR *compliance OR *concordance OR "medication possession ratio" OR MPR OR PDC OR "proportion of days covered")

Appendix B: Schooling effects in difference in difference designs

Assumptions about effects:

- V = VBID effect
- S = Independent schooling effect
- VS = VBID-schooling interaction effect
- T_S = Trend effect of schooling after a defined period. Assume that this period equals both, the follow up, and the period during which schooling was already implemented before VBID implementation.

VBID + S_{new} vs U + S_{new}	Pre implementation	Post implementation
Treatment group	0	$V + S + VS + T_S$
Control group	0	S

Difference in difference = $(V + S + VS + T_S) - S = V + VS + T_S$

VBID + S_{old} vs U + S_{old}	Pre implementation	Post implementation
Treatment group	$S + T_S$	$V + S + VS + 2T_S$
Control group	$S + T_S$	$S + 2T_S$

Difference in difference = $((V + S + VS + 2T_S) - (S + T_S)) - ((S + 2T_S) - (S + T_S)) = V + VS$

VBID + S_{old} vs U	Pre implementation	Post implementation
Treatment group	$S + T_S$	$V + S + VS + 2T_S$
Control group	0	0

Difference in difference = $(V + S + VS + 2T_S) - (S + T_S) - 0 = V + VS + T_S$

Appendix C: Definition of levels of aggregation

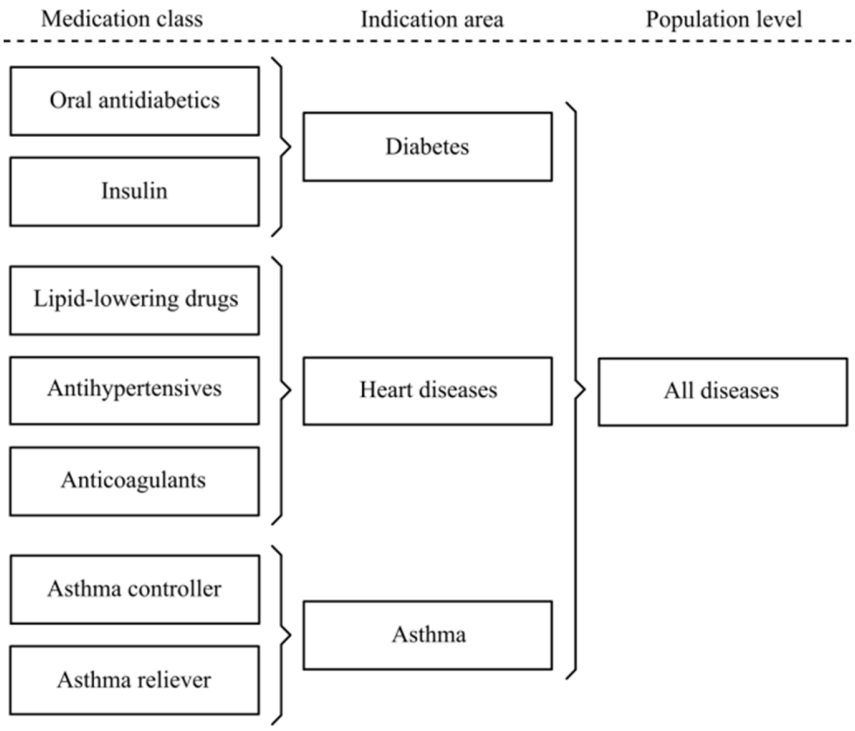

Fig. A1 Levels of aggregation

Medication class	Examples for drugs within one medication class
Oral antidiabetics	Any oral antidiabetic, e.g. metformin
Insulin	Any injected insulin
Lipid-lowering	e.g. statins, CAI
Antihypertensives	e.g. ACEi, ARB, BB, CCB, thiazides, diuretics
Anticoagulants	e.g. clopidogrel
Asthma controller	e.g inhaled steroids
Asthma reliever	Any short acting asthma reliever

CAI = cholesterol absorbing inhibitor, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker, BB = beta blocker, CCB = calcium channel blockers

Table A1 Definition of medication classes

Appendix D: Risk of bias

Population IDs	Author, year, Cit.No	Random sequence generation	allocation concealment	baseline outcome similar, or appropriately adjusted	Baseline characteristics similar	Incomplete outcome data	Knowledge of the allocated interventions adequately prevented during study	protection against contamination	selective outcome reporting	other risks of bias	Excluded in primary meta-analysis
Randomized controlled trails											
MI FREEE, 2007	Choudhry, Avorn, 2011, [1]	L	L	U	U	L	L	L	L	L	
CHORD, 2 ambulatory clinics, 2005	Volpp, Troxel, 2015, [2]	L	L	L	L	L	L	H	L	H	X
Interrupted time series											
Pitney Bowes, 2007	Choudhry, Fischer, 2010, [3]	H	H	L	H	U	L	L	L	L	
Retrospective controlled before-after studies											
Caremark, 2007	Chang, Liberman, 2010, [4]	H	H	L	H	U	L	L	L	L	
ActiveHealth Management, 2005	Chernew, Shah, 2008, [5]	H	H	L	H	U	L	L	L	L	
ZCP, 2010	Clark, DuChane, 2014, [6]	H	H	L	L	L	L	L	L	H[a]	X
Medical Dedication, 2008	Farley, Wansink, 2012, [7]	H	H	L	U	U	L	L	L	L	
	Maciejewski, Farley, 2010, [8]	H	H	L	U	U	L	L	L	L	
	Maciejewski, Wansink, 2014, [9]	H	H	L	U	U	L	L	L	L	
Health Alliance Medical Plans, 2008	Frank, Fendrick, 2012, [10]	H	H	L	U	U	L	L	L	L	
A large multi-industry firm, DMP, diabetes, 2006	Gibson, Mahoney, 2011, [11]	H	H	L	L	U	L	L	L	L	
A large multi-industry firm, DMP, asthma, 2006	Mahoney, Lucas, 2013, [12]	H	H	L	H	U	L	L	L	L	
A large pharmaceutical firm, 2005	Gibson, Wang, 2011, [13]	H	H	L	H	U	L	L	L	L	
Health Enhancement Program, 2011	Hirth, Cliff, 2016, [14]	H	H	L	H	U	L	L	L	L	
Nurse Counseling, 2008; Health Educational Mailings, 2008	Kim, Loucks, 2011, [15]	H	H	L	H	U	L	L	L	H[a]	X
A large employer, 2010	Musich, Wang, 2015, [16]	H	H	L	L[b]	U	L	L	L	L	
A large employer, 2010	Musich, Wang, 2015, [16]	H	H	L	H[c]	U	L	L	L	L	
Kaiser Permanente of Northern California, 2014	Reed, Warton, 2017, [17]	H	H	L	H	U	L	L	L	H	X
Zocor's patent expiration, 2006	Sedjo, Cox, 2008, [18]	H	H	L	H	U	L	H	L	H	X
CPCP DCP, 2008; HHCP, 2008	Wertz, Hou, 2012, [19]	H	H	L	L	U	L	L	L	H[a]	X

[a] Self-selection of patients to control group
[b] In diabetes cohort
[c] In hypertension cohort
Risk of bias: L = low, U = unclear, H = high

Table A2 Risk of bias

Appendix E: Details of schooling and VBID interventions

Population ID[a]	Author, year	Schooling interventions [b]				VBID interventions	
		Treatment group	Inclusion of all group members	Control group	Inclusion of all group members	Treatment group	Control group
Randomized controlled trial							
MI FREEE, 2007[c]	Choudhry, Avorn, 2011, [1]	information about importance of medication adherence	Yes; all patients contacted	information about importance of medication adherence	Yes; all patients contacted	Full coverage for drugs prescribed after myocardial infarction.	No change in copay
CHORD, 2 ambulatory clinics, 2005	Volpp, Troxel, 2015, [2]	An informational video including a testimonial from a patient who realized the importance of adherence	Yes; it was stated that all patients watched that video	Same schooling as treatment group	Yes; it was stated that all patients watched that video	Full coverage for antihypertensive medication.	No change in copay
Interrupted time series							
Pitney Bowes, statins, 2007 Pitney Bowes, clopidogrel, 2007	Choudhry, Fischer, 2010, [3]	A voluntary DMP (no details are reported)	Yes; selection of patients who voluntarily participated at DMP	Not reported	/	Full coverage for statins for patients with diabetes or cardiovascular diseases. Clopidogrel copayment was lowered.	Not reported, but control group has the same benefit manager as intervention group
Retrospective controlled before-after study							
Caremark, 2007	Chang, Liberman, 2010, [4]	Plans with DMP were excluded	/	Plans with DMP were excluded	/	Copay generic diabetics: $15 lowered to $0 per 30-day prescription; preferred brand drugs $30 lowered to ($10-15)	No change in copayment ($10 for generics and preferred brand)
ActiveHealth Management, 2005	Chernew, Shah, 2008, [5]	Nurse led telephone intervention, linked to "clinical alerting" program which is run every month to remind patients and physicians about improvement strategies	No; voluntary program[c]	Same schooling as treatment group	No; voluntary program[c]	Generics $5 lowered to $0; preferred brand-name drugs $25 lowered to $12.50, non-preferred brand-name drugs $45 lowered to 22.50	No change in copayment
ZCP, 2010	Clark, DuChane, 2014, [6]	Disease management and/or wellness programs	Yes; participation is a precondition for VBID participation	No schooling program reported	/	Full coverage: generics, preferred brand and non-preferred brand	No change in copay
Medical Dedication, 2008	Farley, Wansink, 2012, [7] Maciejewski, Farley, 2010, [8] Maciejewski, Wansink, 2014, [9]	Some patients already received DMPs at baseline (no details on programs are reported)	No; voluntary program[c]	Some patients already received DMPs at baseline (no details on programs are reported)	No; voluntary program[c]	Full coverage for generic drugs prescribed for diabetes, hypertension, hyperlipidemia, congestive heart failure; lowered from tier 3 to tier 2: metformin, statins, thiazide diuretics, ACEis, beta-blockers, CCBs, ARBs	Lowered from tier 3 to tier 2: metformin, statins, thiazide diuretics, ACEIs, beta-blockers, CCBs, ARBs
Health Alliance Medical Plans, 2008	Frank, Fendrick, 2012, [10]	No schooling interventions are reported	/	No schooling interventions are reported	/	reduced copay for brand statins by 42,9%	Increased copay for brand statins by 16.7%

Population ID[a]	Author, year	Schooling interventions [b]				VBID interventions	
		Treatment group	Inclusion of all group members	Control group	Inclusion of all group members	Treatment group	Control group
A large multi-industry firm, DMP, diabetes, 2006	Gibson, Mahoney, 2011, [11]	Targeted and educational mailings, workbook, telephone calls from a nurse, coaching, regular monitoring	Yes; patients who opted into the program were selected	Same intervention as treatment group	Yes; patients who opted into the program were selected	All tiers are reduced to 10% copay	No change in copay
A large multi-industry firm, DMP, asthma, 2006	Mahoney, Lucas, 2013, [12]	Targeted and educational mailings, workbook, telephone calls from a nurse, coaching, regular monitoring	Yes; patients who opted into the program were selected	Same intervention as treatment group	Yes; patients who opted into the program were selected	All tiers are reduced to 10% copay	No change in copay
A large pharmaceutical firm, 2005	Gibson, Wang, 2011, [13]	DMP	No; voluntary DMP	No schooling interventions are reported	/	Copay was reduced for asthma, selected cardiovascular, diabetes and hypertension medication to 10% for retail prescription and 7.5% for mail-order prescriptions.	No value based-cost sharing
Health Enhancement Program, 2011	Hirth, Cliff, 2016, [14]	DMP includes risk assessments, physical examinations, screenings, reminders and further financial incentives for adherent participation	Yes; participation is a precondition for VBID	No schooling interventions are reported	/	Reduction of copay or full coverage for chronic diseases (asthma, COPD, diabetes, heart disease, hypertension, hyperlipidemia); full coverage for all diabetes medications and for generics prescribed for chronic diseases; new $35 copay for emergency department visits with reasonable alternative	No major structural change
Nurse Counseling, 2008	Kim, Loucks, 2011, [15]	Nurse counseling	Yes; participation is a precondition for VBID	No schooling, employers denied program participation	/	Reduction of copay in a four-tier insurance design, lowered to $0 – 25 for 30-day supply and to $0 – 55 for 90-day supply	No change in benefit design
Health Educational Mailings, 2008		Health educational mailings	Yes; participation is required for VBID participation	No schooling, employers denied program participation	/		
A large employer, 2010	Musich, Wang, 2015, [16]	Health and disease coaching program	Yes; participation is a precondition for inclusion	Same intervention as treatment group	Yes; participation is a precondition for inclusion	Full coverage for generics for chronic diseases (diabetes, hypertension), reduced copayment for brand drugs: preferred brand drugs $5 for 34-day supply, $15 for 90-days of supply, non-preferred brand drugs: 50% coinsurance with min/max levels of copay	No change in cost-sharing
Kaiser Permanente of Northern California, 2014	Reed, Warton, 2017, [17]	No schooling interventions are reported	/	No schooling interventions are reported	/	Full coverage for selected preventive medication (e.g. diabetes, hypertension, hyperlipidemia)	No change in copay
Zocor's patent expiration, 2006	Sedjo, Cox, 2008, [18]	No schooling interventions are reported	/	No schooling interventions are reported	/	Reduced copay because of patent expirations which causes a switch in tiers	No change[d]
CPCP DCP, 2008	Wertz, Hou, 2012, [19]	Regular meeting with community based pharmacists	Yes; meetings are a part of CPCP	No meetings, employees denied participation	/	Full coverage for diabetes, hypertension, dyslipidemia	No change in copay
CPCP HHCP, 2008		Regular meeting with community based pharmacists	Yes; meetings are a part of CPCP	No meetings, employees denied participation	/	Full coverage for diabetes, hypertension, dyslipidemia	No change in copay

[a] Name of VBID program or provider, population, year of VBID implementation
[a] Schooling with or without further diseases management interventions
[b] Cluster randomized trial
[c] The proportions of participants were similar between groups at baseline and at follow up
[d] Patients in control group received a generic statin before the patient expiration and are therefore not affected by the copay change in the treatment group.
ACEi = ACE inhibitor, ARB = angiotensin-receptor blocker, BB = beta-blocker, CAI = cholesterol absorbing inhibitor, CCB = calcium channel blockers, CG = control group, Cit. No. = citation number, CPCP = Cincinnati pharmacy coaching program, DCP = diabetes coaching program, DMP = disease management program, FU = follow up, HHCP = healthy heart coaching program, MTM = medication therapy management, S_{new} = newly implemented schooling intervention, VBID = value based health insurance design, ZCP = zero copay program

Table A3 Details of schooling and VBID interventions

Appendix F: Sensitivity analyses

Forest plot including all populations identified for this review

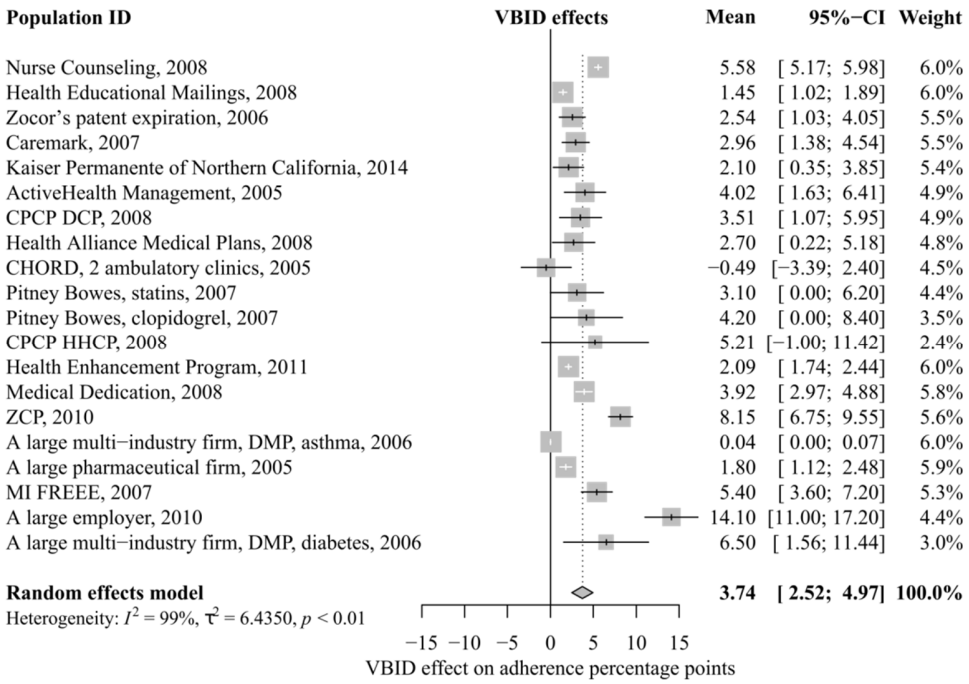

Fig. A2 Forest plot including all populations identified for this review

Adjusted VBID effects on adherence

Meta-regression models	Outlier excluded			Effects with high risk of bias are included		
	K	VBID effect [a]	p-value	K	VBID effect [a]	p-value
Model 1: population level [b]	17			27		
Mean VBID effect		2.09**	<0.01		3.05***	<0.01
Model 2: indication area [c]	29			45		
Time trend effect per year		0.15**	<0.01		0.16**	<0.01
Asthma		2.09***	<0.01		3.12***	<0.01
Diabetes		1.85***	<0.01		2.98***	<0.01
Heart diseases		2.98***	<0.01		3.55***	<0.01
Model 3: medication class [d]	28			47		
Anticoagulants		3.92	0.11		3.95	0.33
Antihypertensive		1.22	0.08		1.96*	0.04
Asthma controller		2.10**	<0.01		2.98**	<0.01
Asthma reliever		-0.81	0.55		-0.72	0.84
Insulin		1.75	0.10		3.10**	<0.01
Lipid-lowering medication		3.23***	<0.01		3.92***	<0.01
Oral antidiabetics		3.05***	<0.01		5.12***	<0.01

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05
[a] VBID effect on adherence percentage points
[b] Overall VBID effect on adherence across all indications and VBID programs, adjusted by time trend effects and random population effects.
[c] VBID time trend effect on adherence per year and mean VBID effect on adherence to drugs prescribed for different indications, adjusted by random population effects.
[d] VBID effect on adherence to different drugs, adjusted by time trend effects and random population effects.
K = number of effects included, VBID = value based health insurance design

Table A4 Adjusted VBID effects on adherence – influential analyses

	VBID effect estimates		
	r = 0.0	r = 0.5	r = 1
Model 1: population level [a], K = 19			
Mean VBID effect	3.36**	3.24**	3.15**
Model 2: indication area [b], K = 29			
Time trend effect per year	0.16**	0.16**	0.15**
Asthma	3.13**	3.15**	3.17**
Diabetes	2.89**	2.91**	2.92**
Heart diseases	4.01***	4.03***	4.06***
Model 3: medication class [c], K = 31			
Anticoagulants	4.05	4.02	4.01
Antihypertensives	2.69	2.67	2.66
Asthma controller	3.65*	3.58*	3.53*
Asthma reliever	-0.43	-0.49	-0.53
Insulin	3.17	3.12	3.09
Lipid-lowering medication	4.74**	4.69**	4.65**
Oral antidiabetics	4.67**	4.62**	4.59**

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05
[a] Overall VBID effect on adherence across all indications and VBID programs, adjusted by time trend effects and random population effects.
[b] VBID time trend effect on adherence per year and mean VBID effect on adherence to drugs prescribed for different indications, adjusted by random population effects.
[c] VBID effect on adherence to different drugs, adjusted by time trend effects and random population effects.
K = number of effects included, r = correlation between outcomes within in the same population, VBID = value based health insurance design

Table A5 Adjusted VBID effects on adherence – varying correlation between adherence outcomes

VBID effects on adherence in different VBID incentive designs

	Exclusion of outlier: "A large employer, 2010"				Inclusion of all references identified in this review			
Subgroup analyses	K	VBID effect [a]	95% CI, p-value	τ^2	K	VBID effect [a]	95% CI, p-value	τ^2
Any schooling effect								
Yes	9	3.00	[1.69; 4.31]	2.93	16	4.06	[2.67; 5.46]	6.63
No	2	2.89	[1.55; 4.22]	0	4	2.58	[1.71; 3.45]	0
Q-test for subgroup differences			p = 0.9039				p = 0.0766	
Individualization of schooling [b]								
Yes	8	2.65	[1.31; 3.99]	2.64	13	4.57	[2.86; 6.27]	8.15
No	3	3.75	[2.02; 5.48]	1.36	7	2.46	[1.32; 3.60]	1.55
Q-test for subgroup differences			p = 0.3225				p = 0.0440	
Full coverage								
Yes	7	3.39	[2.31; 4.47]	1.34	15	4.13	[2.87; 5.39]	5.00
No	4	1.81	[0.08; 3.54]	1.92	5	2.02	[0.46; 3.57]	2.07
Q-test for subgroup differences			p = 0.1287				p = 0.0387	

[a] VBID effect on adherence percentage points
[c] Individualized schooling = the program included at least individualized information or complex disease management; no individualized schooling = standardized schooling or no schooling is combined with VBID.
CI = confidence interval, K = number of effects, VBID = value based health insurance design

Table A6 Subgroup differences between VBID incentive designs - influential analyses

p-values from subgroup meta-analyses on population level	p-values			
	r = 0	r = 0.5	r = 0.8	r = 1
Any schooling effect	0.2996	0.2847	0.2781	0.2746
Individualized schooling	0.9309	0.9701	0.9909	0.9967
Full coverage vs reduced cost-sharing only	0.0230	0.0256	0.0272	0.0281

r = correlation between outcomes within the same population

Table A7 Tests for subgroup differences - varying correlation between adherence outcomes

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