

scientific reports



OPEN

Polypill eligibility and equivalent intake in a Swiss population-based study

Julien Castioni^{1,2}, Nazanin Abolhassani^{1,2}✉, Peter Vollenweider¹, Gérard Waeber¹ & Pedro Marques-Vidal¹

The polypill has been advocated for cardiovascular disease (CVD) management. The fraction of the population who could benefit from the polypill in Switzerland is unknown. Assess (1) the prevalence of subjects (a) eligible for the polypill and (b) already taking a polypill equivalent; and (2) the determinants of polypill intake in the first (2009–2012) and second follow-ups (2014–2017) of a population-based prospective study conducted in Lausanne, Switzerland. The first and the second follow-ups included 5038 and 4596 participants aged 40–80 years, respectively. Polypill eligibility was defined as having a high CVD risk as assessed by an absolute CVD risk $\geq 5\%$ with the SCORE equation for Switzerland and/or presenting with CVD. Four polypill equivalents were defined: statin + any antihypertensive with (A) or without (B) aspirin; statin + calcium channel blocker (CCB) (C); and statin + CCB + angiotensin-converting enzyme inhibitor (D). The prevalence of polypill eligibility was 20.6% (95% CI 19.5–21.8) and 27.7% (26.5–29.1) in the first and second follow-up, respectively. However, only around one-third of the eligible 29.5% (95% CI 26.7–32.3) and 30.4% (27.9–33.0) respectively, already took the polypill equivalents. All polypill equivalents were more prevalent among men, elderly and in presence of CVD. After multivariable adjustment, in both periods, male gender was associated with taking polypill equivalent A (OR: 1.93; 95% CI 1.45–2.55 and OR: 1.67; 95% CI 1.27–2.19, respectively) and polypill equivalent B (OR: 1.52; 95% CI 1.17–1.96 and OR: 1.41; 95% CI 1.07–1.85, respectively). Similarly, in both periods, age over 70 years, compared to middle-age, was associated with taking polypill equivalent A (OR: 11.71; CI 6.74–20.33 and OR: 9.56; CI 4.13–22.13, respectively) and equivalent B (OR: 13.22; CI 7.27–24.07 and OR: 20.63; CI 6.51–56.36, respectively). Former or current smoking was also associated with a higher likelihood of taking polypill equivalent A in both periods. A large fraction of the population is eligible for the polypill, but only one-third of them actually benefits from an equivalent, and this proportion did not change over time.

Abbreviations

MI	Myocardial infarction
ACEi	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptors blockers
CCB	Calcium-channel blockers
BB	Beta-blockers
antiHTA	Antihypertensive
CVD	Cardiovascular disease
FDC	Fixed dose combination

Cardiovascular disease (CVD) is the major cause of death and disability worldwide¹. The reduction of CVD burden requires strategies that are applied to the entire or to large segments of the population². Despite effective cardiovascular drugs, adherence is suboptimal in both primary and secondary prevention³. The “polypill”, a fixed dose combination of statin, one or more anti-hypertensive drugs with or without aspirin, could increase adherence^{4,5} and reduce CVD burden^{6,7}. Several strategies have been proposed for using the polypill: mass treatment for all elderly subjects^{8,9}; primary prevention among subjects at high CVD risk¹⁰, and secondary prevention among patients with established CVD¹¹. Which strategy is the best is still under debate¹². Currently, it is estimated

¹Department of Medicine, Internal Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ²These authors contributed equally: Julien Castioni and Nazanin Abolhassani. ✉email: nazanin.abolhassani@unisante.ch

that a sizable fraction of the general population is already taking the polypill components as separate drugs. Replacing these separate drugs by a fixed dose combination (polypill) could improve adherence to treatment and reduce CVD. There are different types of polypill equivalents available^{13,14}, but the fraction of the population who could (1) benefit from the polypill or (2) who is already taking the polypill components (i.e., a polypill equivalent) as separate drugs is largely unknown.

This study aimed to assess (1) the prevalence of subjects (a) eligible for the polypill and (b) already taking a polypill equivalent; and (2) the determinants of polypill intake in the first (2009–2012) and second follow-up (2014–2017) of a prospective population-based study conducted in Lausanne, Switzerland. We also assessed which components of the different polypills were already prescribed.

Materials and methods

Study population and design. The ColaUS/PsyColaUS study (<http://www.colaus-psycolaus.ch>) is an ongoing prospective survey investigating the biological and genetic determinants of CV risk factors and CVD in the population of Lausanne, Switzerland. Detailed descriptions of the study design have been reported elsewhere¹⁵. In summary, a non-stratified random sample of the overall population of Lausanne aged between 35 and 75 years was drawn. The following inclusion criteria were applied: (a) written informed consent; (b) willingness to take part in the examination and to provide blood samples. Recruitment began in June 2003 and ended in May 2006 and included 6733 participants. Participation rate was 41%. The evaluation included an interview, a physical exam, blood sampling and a set of questionnaires.

The follow-up visit was similar to the baseline evaluation and was performed between April 2009 and September 2012, five and a half years on average after the collection of baseline data, and 5064 subjects participated; out of them, 5038 (99.5%) who had CVD risk data were included in this study. Similarly, for the second follow-up (2014–2017), 4881 subjects participated; out of them 4596 (94.2%) who had CVD risk data were included in the study. The data from the first and second follow-ups were used in this study (Supplemental Figure 1, panels A and B, respectively).

Data collected. CVD, lifestyle and medication status were assessed by questionnaire. CVD was defined as personal history of myocardial infarction (MI), unstable or stable angina, coronary artery bypass grafting, stroke, transient ischemic attack or peripheral arterial disease. Whenever possible, CVD reported by participants was documented and adjudicated by an independent panel of experts. Smoking status was categorized into never, former and current as reported. Medications were assessed by questionnaire and further confirmed by interview, where subjects were asked to provide the names of all prescribed and over-the-counter drugs regularly taken over the last 6 months. No specific information was collected whether it was the general practitioner or the cardiologist who prescribed the medications.

Polypill eligibility was defined as presenting with previous CVD (secondary prevention) or, in the absence of CVD, an absolute CVD risk $\geq 5\%$ assessed by the SCORE equation for Switzerland¹⁶ (primary prevention). Four commercially available polypill equivalents were defined: equivalent A: aspirin + statin + any antihypertensive; equivalent B: no aspirin + statin + any antihypertensive; equivalent C: no aspirin + statin + calcium channel blocker (equivalent to Caduet in Switzerland); equivalent D: no aspirin + statin + calcium channel blocker + angiotensin-converting enzyme inhibitor (equivalent to Triveram in Switzerland). The last two are the only approved polypills in Switzerland.

Statistical analysis. Statistical analyses were conducted separately for each survey period (2009–2012 and 2014–2017). Analyses were performed using STATA software 16.0 (Stata Corp, College Station, TX, USA). Descriptive results were expressed as number of participants (percentage) for all categorical variables. Exact Poisson confidence intervals for prevalence rates for polypill eligibility and for each polypill equivalent were obtained using the `ci proportions` command of Stata. Bivariate analysis comparing the distribution of the different covariates (i.e. gender, age group...) within each polypill equivalent (use/non-use) was performed using chi-square or Fisher's exact test. Multivariate analysis assessing which covariates were associated with use of each polypill equivalent was conducted using logistic regression with the polypill equivalent (use/non-use) as dependent variable and gender (man, woman), age group ([40–50], [50–60], [60–70], [70+]), smoking status (never, former, current) and history of CVD (yes, no) as independent variables. Results were expressed as odds ratio (OR) and 95% confidence interval (CI). A two-sided test p-value below 0.05 was considered statistically significant.

Ethical statement. The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (<http://www.cer-vd.ch>) approved the baseline CoLaUS study (reference 16/03). The approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-ups. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. Written informed consent was obtained from all participants.

Results

Characteristics of the participants. The characteristics of the included and excluded participants are summarized in supplemental Table 1. In the first follow-up, of the 5064 participants available, 26 (0.5%) were excluded; no differences were found between included and excluded participants. In the second follow-up, of the 4881 participants available, 285 (5.8%) were excluded; excluded participants were more frequently in the age group [60–70] and less frequently former smokers than included participants.

	2009–2012	2014–2017
Polypill eligibility		
All	20.6 (19.5–21.8)	27.7 (26.5–29.1)
Primary prevention	12.8 (11.9–13.7)	16.5 (15.4–17.6)
Secondary prevention	7.8 (7.1–8.6)	11.3 (10.4–12.2)
Polypill equivalents intake among eligible		
Any	29.5 (26.7–32.3)	30.4 (27.9–33.0)
Equivalent A ^a	19.7 (17.4–22.3)	19.0 (16.9–21.2)
Equivalent B ^b	9.7 (8.0–11.7)	11.5 (9.8–13.3)
Equivalent C ^c	6.6 (5.2–8.3)	7.4 (6.0–8.9)
Equivalent D ^d	2.6 (1.7–3.8)	2.0 (1.3–2.9)

Table 1. Prevalence of polypill eligibility and of the different polypill equivalents, Colaus study, Lausanne, Switzerland, 2009–2012 and 2014–2017. Results are expressed as percentage and 95% confidence interval. ^aAspirin + statin + any antihypertensive. ^bNo aspirin + statin + any antihypertensive. ^cNo aspirin + statin + calcium channel blocker (equivalent to Caduet in Switzerland). ^dNo aspirin + statin + calcium channel blocker + angiotensin-converting enzyme inhibitor (equivalent to Triveram in Switzerland).

Prevalence of polypill eligibility and polypill equivalents. The distribution of eligibility and any polypill equivalents intake are summarized in supplemental Table 2. Prevalence of polypill (primary and secondary) eligibility and of the different polypill equivalents is summarized in Table 1. The prevalence of polypill eligibility, based on previous CVD or a CVD SCORE risk $\geq 5\%$, increased from one-fifth in the first follow-up to over one quarter of participants in the second. The majority of eligible subjects were in the primary prevention arm. The prevalence of eligible subjects taking polypill components was lower and around one-third of the eligible subjects in the first and second follow-up. Polypill equivalent A had the highest prevalence in both periods, followed by B, C and D.

Determinants of polypill equivalent use. The bivariable and multivariable associations between selected sociodemographic and clinical variables and the type of polypill equivalent used are summarized in Tables 2 and 3, respectively. Irrespective of the type of polypill equivalent, in both periods, the prevalence was higher among men, the elderly and participants with a history of CVD (Table 2). After multivariable adjustment, male gender, increasing age or history of CVD were associated with a higher likelihood of taking polypill equivalents A or B in both periods, and former or current smokers with a higher likelihood of taking polypill equivalent A in both periods (Table 3).

Distribution of polypill components. The distribution of polypill components is summarized in supplemental Table 3. The most prescribed component was antihypertensive drugs, of which the most prescribed were angiotensin receptor blockers, followed by beta-blockers. Statins were the most frequent prescribed hypolipidaemic drug and aspirin was the most frequently prescribed antiplatelet drug.

Discussion

In this population-based study, over one-fifth and one-fourth of the participants were eligible for a polypill in two time points 5 years apart. Nevertheless, only one-third of them actually benefits from an equivalent, and this proportion did not change over time. Male gender, increasing age or history of CVD were associated with a higher likelihood of taking a polypill equivalent.

Prevalence of polypill eligibility and polypill intake. The eligibility for polypill is a matter of debate, especially in primary prevention, and can explain the low prevalence of polypill equivalent in our study in comparison to eligible subjects, based on the SCORE equation for Switzerland and previous CVD¹⁶. In comparison, the intake of polypill components was also low in a study in the US, which considered age ≥ 55 years and a history of CVD as polypill eligibility criteria. They showed that 37.3% of US adults ≥ 55 years and 57.0% of those with a history of CVD were taking statins and the use of other polypill medications was also low¹⁷. Such results can be comparable with ours and the higher intake of polypill can be due to the different eligibility criteria. The difference between use of polypill in secondary, compared to the primary prevention, was lower which can be due to the broader support for the use of polypill in secondary prevention of CVD¹⁸. Our results imply a gap between an individual cardiovascular risk target approach and a population-based global strategy that should co-exist to tackle the burden of CVD.

Although polypills have been approved in more than 30 countries and the effectiveness in preventing major CV events, increasing medication adherence and lowering number of adverse events has been reported, their availability remains limited^{13,19}. A large availability, with many types and doses combination, is essential for polypill in primary high risk and secondary prevention as demonstrated in an Australian study, where, even if 62.4% of the patients were still taking the polypill after 18 months, 47.4% of them had additional classes of antihypertensive drugs prescribed⁵. Even considering only fixed drug combination for antihypertensive therapy,

	2009–2012				2014–2017			
	A	B	C	D	A	B	C	D
Gender								
Woman	97 (3.6)	119 (4.4)	46 (1.7)	12 (0.5)	119 (4.7)	128 (5.1)	59 (2.3)	15 (0.6)
Man	182 (7.8)	144 (6.1)	81 (3.5)	28 (1.2)	204 (9.9)	138 (6.7)	84 (4.1)	22 (1.1)
p-value	<0.001	0.006	<0.001	0.003	<0.001	0.021	0.001	0.077
Age group								
[40–50]	16 (1.1)	13 (0.9)	9 (0.6)	3 (0.2)	6 (1.1)	3 (0.5)	1 (0.2)	1 (0.2)
[50–60]	44 (2.9)	50 (3.3)	25 (1.6)	8 (0.5)	37 (2.5)	38 (2.6)	11 (0.8)	1 (0.1)
[60–70]	101 (7.5)	118 (8.8)	43 (3.2)	8 (0.6)	83 (6.8)	74 (6.1)	34 (2.8)	10 (0.8)
[70+]	118 (16.0)	82 (11.1)	50 (6.8)	21 (2.9)	197 (14.7)	151 (11.3)	97 (7.2)	25 (1.9)
p-value	<0.001	<0.001	<0.001	<0.001 [§]	<0.001	<0.001	<0.001	<0.001 [§]
Smoking status								
Never	72 (3.6)	103 (5.1)	40 (2.0)	8 (0.4)	81 (4.6)	107 (6.0)	46 (2.6)	11 (0.6)
Former	155 (8.3)	113 (6.0)	62 (3.3)	23 (1.2)	158 (9.3)	99 (5.9)	57 (3.4)	16 (1.0)
Current	51 (4.7)	47 (4.3)	25 (2.3)	9 (0.8)	61 (7.7)	38 (4.8)	25 (3.1)	5 (0.6)
p-value	<0.001	0.125	0.026	0.014	<0.001	0.430	0.386	0.483
History of CVD								
No	192 (3.9)	242 (5.0)	97 (2.0)	29 (0.6)	173 (4.1)	217 (5.1)	103 (2.4)	21 (0.5)
Yes	87 (52.7)	21 (12.7)	30 (18.2)	11 (6.7)	150 (43.6)	49 (14.2)	40 (11.6)	16 (4.7)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 2. bivariate associations between selected clinical variables and type of polypill equivalent, CoLaus study, Lausanne, Switzerland, 2009–2012 and 2014–2017. Results are expressed as number (row percentage). Equivalent A: aspirin + statin + any antihypertensive; equivalent B: no aspirin + statin + any antihypertensive; equivalent C: no aspirin + statin + calcium channel blocker; equivalent D: no aspirin + statin + calcium channel blocker + angiotensin-converting enzyme inhibitor. Between-group comparisons performed using chi-square or Fisher's exact test (§).

	2009–2012		2014–2017	
	Polypill equivalent A	Polypill equivalent B	Polypill equivalent A	Polypill equivalent B
Gender				
Woman	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Man	1.93 (1.45–2.55)	1.52 (1.17–1.96)	1.67 (1.27–2.19)	1.41 (1.07–1.85)
Age group				
[40–50]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
[50–60]	2.27 (1.26–4.08)	3.64 (1.97–6.74)	1.91 (0.79–4.62)	4.76 (1.46–15.50)
[60–70]	5.83 (3.37–10.06)	10.48 (5.87–18.72)	4.76 (2.03–11.17)	11.15 (3.49–35.64)
[70+]	11.71 (6.74–20.33)	13.22 (7.27–24.07)	9.56 (4.13–22.13)	20.63 (6.51–65.36)
p-value for trend	<0.001	<0.001	<0.001	<0.001
Smoking status				
Never	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Former	1.86 (1.35–2.55)	0.99 (0.74–1.31)	1.69 (1.24–2.31)	0.81 (0.60–1.08)
Current	1.60 (1.10–2.39)	0.98 (0.68–1.41)	2.11 (1.43–3.10)	0.89 (0.60–1.31)
p-value for trend	0.023	0.920	<0.001	0.549
History of CVD				
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	14.65 (10.21–21.02)	1.50 (0.92–2.46)	12.34 (9.23–16.50)	1.93 (1.33–2.78)

Table 3. Multivariable association between selected clinical variables and type of polypill equivalent, CoLaus study, Lausanne, Switzerland, 2009–2012 and 2014–2017. Results are expressed as odds ratio (95% confidence interval). Equivalent A: aspirin + statin + any antihypertensive; equivalent B: no aspirin + statin + any antihypertensive. Statistical analysis using logistic regression. Significant ($p < 0.05$) odds ratios are indicated in bold.

availability remains poor. For example, in an American study, the most frequently filled fixed drug combination lisinopril/HCTZ was marketed only in 3 doses, although 20 combinations are possible²¹. In the Swiss market, no polypill with aspirin exists although more than one out of 20 participants could benefit from it, and only two equivalents without aspirin exist (C and D). This underlines the potential benefits of a larger availability of a polypill in Switzerland to improve adherence in primary or secondary preventive approach.

Determinants of polypill equivalents intake. Male gender, increased age and previous history of CVD were associated with higher frequency of the polypill equivalents intake; this observation is consistent with gender and age differences in CVD risk factors^{16,20}. For polypill equivalent A (aspirin + statin + any hypertensive drugs), also a positive association with smoking and previous history of CVD was found in both first and second follow-ups. For polypill equivalent B (no aspirin + statin + any hypertensive drugs), the association with previous history of CVD was only significant in the second follow-up.

Prevalence of polypill components. Antihypertensive drugs are the most frequently prescribed polypill component (one quarter of the subjects). This could reflect the high proportion of hypertension in the Swiss population, estimated as 36%²¹, and a high adherence to hypertension target treatment recommendations²². Regarding antihypertensive drug treatment, studies showed polypills containing multiple low doses of BP-lowering drugs produce more effective BP lowering than the use of fewer separate BP-lowering drugs at higher doses, without an increase in adverse effects^{7,18}. In our study, angiotensin receptor blockers were the most used hypertensive drug class. It is quite different from other studies where ACEi inhibitors were the most frequently prescribed class, as shown in an Australian study comparing the adherence of high risk and established CV patients to a polypill group (simvastatin, lisinopril and atenolol or HCTZ) vs standard medication group⁵. In this study, all patients were treated by one of the 38 different blood pressure-lowering medications. ACE inhibitors are the most prescribed followed by BB and then ARB. In USA, Wang et al. examined prescriptions fill rates for dyslipidemia, diabetes and hypertension treatments using claims data from a large national insurer for > 14 million people²³. The most prescribed combination was a statin and hypertensive molecule of which ACEi was the most frequent, followed by BB, CCB and ARB. The switch between ACEi and ARB between our study and two others could be explained by the higher risk profile of the subjects in the mentioned studies. Also, easy access to and marketing of ARB in Switzerland could play a role. Aspirin is much more frequent than other antiplatelet medications as it is the only one to be indicated in primary prevention. Statins are by far the most prescribed hypolipidaemic drug class according to the Swiss atherosclerosis association Swiss recommendations (<http://www.gsla.ch>). Nevertheless, another study in Switzerland also showed no parallel increase in hypolipidemic drugs along with increased dyslipidaemia prevalence and its management remained far from optimal in both primary and secondary prevention²⁴. Also, a study in 78 centers from 16 European countries revealed that large proportions of people at high CVD risk have inadequate control of blood pressure, lipids and diabetes²⁵. Suboptimal management of coronary patients was reported in a 24 European countries in 2015²⁶ and further in 27 European countries in 2019²⁷. In addition, there are differences in guidelines of the use of statins in primary prevention in Europe and other countries that could also contribute to the low use of this drug class in this indication^{28,29}.

Strengths and limitations. This study evaluates polypill eligibility in a general population sample of more than 6000 persons. Contrary to the polypill eligibility, we assessed the real life intake of polypill equivalents, defined by the intake of separated components of polypill, and its change in five years.

As limitations, we could cite the selection bias of the general population, described elsewhere¹⁵. In addition, as drugs data were self-reported, it might be prone to recall bias and finally underestimation. However, our results can provide at least an estimation of the real life polypill intake and of the gap to the theoretic eligibility. The results should be interpreted cautiously due to the certain criteria for eligibility that we used in this study i.e. having a high CVD risk and/or presenting with CVD, could be different in other countries and even largely underestimated if following mass treatment criteria as suggested by Wald and colleagues⁹. Using this criterion such as age + 50 years, the theoretic eligibility would be 72% and 88% in the two follow-ups, respectively, and the gap with real life even larger as only about one-seventh of them already taking polypill equivalents at both periods. In addition, we used SCORE for CVF risk stratification, however, GSKA score may be also used in Switzerland. Furthermore, this was a monocentric study and might not be fully generalizable to other places with different health system and availability of polypills. Even, within a country like Switzerland, different prescription prevalence across cantons has been reported³⁰ so generalizability should be considered given such limitations.

Conclusion

In this prospective study in Swiss community-dwelling subjects, over one-fifth and one-fourth were eligible for a polypill. Nevertheless, only one-third of them actually benefits from an equivalent, and this proportion did not change over time.

Received: 8 September 2020; Accepted: 18 January 2021

Published online: 25 March 2021

References

1. Kolte, D., Aronow, W. S. & Banach, M. Polypills for the prevention of cardiovascular diseases. *Expert Opin. Investig. Drugs*. **25**(11), 1255–1264 (2016).
2. Lonn, E. *et al.* The polypill in the prevention of cardiovascular diseases. *Circulation* **122**(20), 2078–2088 (2010).

3. Kotseva, K. *et al.* EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur. J. Prev. Cardiol.* **23**(6), 636–648 (2016).
4. Selak, V. *et al.* Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: Randomised controlled trial in primary care. *BMJ* **348**, g3318 (2014).
5. Truelove, M. *et al.* The effect of a cardiovascular polypill strategy on pill burden. *Cardiovasc. Ther.* **33**(6), 347–352 (2015).
6. Yusuf, S. *et al.* Combination pharmacotherapy to prevent cardiovascular disease: present status and challenges. *Eur. Heart J.* **35**(6), 353–364 (2014).
7. Munoz, D. *et al.* Polypill for cardiovascular disease prevention in an underserved population. *N. Engl. J. Med.* **381**(12), 1114–1123 (2019).
8. Wald, N. J. & Law, M. R. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* **326**(7404), 1419 (2003).
9. Wald, D. S., Morris, J. K. & Wald, N. J. Randomized Polypill crossover trial in people aged 50 and over. *PLoS ONE* **7**(7), e41297 (2012).
10. Thom, S. *et al.* Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: The UMPIRE randomized clinical trial. *JAMA* **310**(9), 918–929 (2013).
11. Becerra, V. *et al.* Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. *BMJ Open.* **5**(5), e007111 (2015).
12. Webster, R., Castellano, J. M. & Onuma, O. K. Putting polypills into practice: Challenges and lessons learned. *Lancet* **389**(10073), 1066–1074 (2017).
13. Huffman, M. D., Xavier, D. & Perel, P. Uses of polypills for cardiovascular disease and evidence to date. *Lancet* **389**(10073), 1055–1065 (2017).
14. Bahiru, E. *et al.* Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. *Cochrane Database Syst. Rev.* **3**, CD009868 (2017).
15. Firmann, M. *et al.* The CoLaus study: A population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc. Disord.* **8**, 6 (2008).
16. Marques-Vidal, P. *et al.* Predictive accuracy and usefulness of calibration of the ESC SCORE in Switzerland. *Eur. J. Cardiovasc. Prev. Rehabil.* **15**(4), 402–408 (2008).
17. Muntner, P. *et al.* Projected impact of polypill use among US adults: Medication use, cardiovascular risk reduction, and side effects. *Am. Heart J.* **161**(4), 719–725 (2011).
18. Chow, C. K. & Meng, Q. Polypills for primary prevention of cardiovascular disease. *Nat. Rev. Cardiol.* **16**(10), 602–611 (2019).
19. Roshandel, G. *et al.* Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): A pragmatic, cluster-randomised trial. *Lancet* **394**(10199), 672–683 (2019).
20. Farhangi, M. A. & Jahangiry, L. Gender difference in the association between Framingham Risk Score with cardio-metabolic risk factors and psychological distress in patients with metabolic syndrome. *Diabetes Metab. Syndr.* **14**(2), 71–75 (2020).
21. Danon-Hersch, N. *et al.* Prevalence, awareness, treatment and control of high blood pressure in a Swiss city general population: The CoLaus study. *Eur. J. Cardiovasc. Prev. Rehabil.* **16**(1), 66–72 (2009).
22. Christe, V., Waeber, G., Vollenweider, P. & Marques-Vidal, P. Antihypertensive drug treatment changes in the general population: The CoLaus study. *BMC Pharmacol. Toxicol.* **15**, 20 (2014).
23. Wang, B., Choudhry, N. K., Gagne, J. J., Landon, J. & Kesselheim, A. S. Availability and utilization of cardiovascular fixed-dose combination drugs in the United States. *Am. Heart J.* **169**(3), 379–86.e1 (2015).
24. Antiochos, P., Marques-Vidal, P., Waeber, G. & Vollenweider, P. Five year trends in dyslipidaemia prevalence and management in Switzerland: The CoLaus study. *Nutr. Metab. Cardiovasc. Dis.* **25**(11), 1007–1015 (2015).
25. Kotseva K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, *et al.* Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. *Eur. J. Prev. Cardiol.* 2020:2047487320908698.
26. Gyberg, V. *et al.* Patients with coronary artery disease and diabetes need improved management: a report from the EUROASPIRE IV survey: A registry from the EuroObservational Research Programme of the European Society of Cardiology. *Cardiovasc. Diabetol.* **14**, 133 (2015).
27. De Backer, G. *et al.* Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis.* **285**, 135–146 (2019).
28. Mortensen, M. B. & Nordestgaard, B. G. Comparison of five major guidelines for statin use in primary prevention in a contemporary general population. *Ann. Intern. Med.* **168**(2), 85–92 (2018).
29. McElduff, P., Jaefarnezhad, M. & Durrington, P. N. American, British and European recommendations for statins in the primary prevention of cardiovascular disease applied to British men studied prospectively. *Heart* **92**(9), 1213–1218 (2006).
30. Luta, X. *et al.* Patterns of benzodiazepine prescription among older adults in Switzerland: A cross-sectional analysis of claims data. *BMJ Open.* **10**(1), e031156 (2020).

Author contributions

J.C. and P.M.V. designed the study; NA made the statistical analyses; N.A. and J.C. wrote the article; P.M.V. collected data, supervised the statistical analysis. P.M.V., G.W. and P.V. revised the article for important intellectual content. P.M.V. had full access to the data and is the guarantor of the study.

Funding

The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 32003B_173092, 33CS30-139468 and 33CS30-148401).

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-021-84455-8>.

Correspondence and requests for materials should be addressed to N.A.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

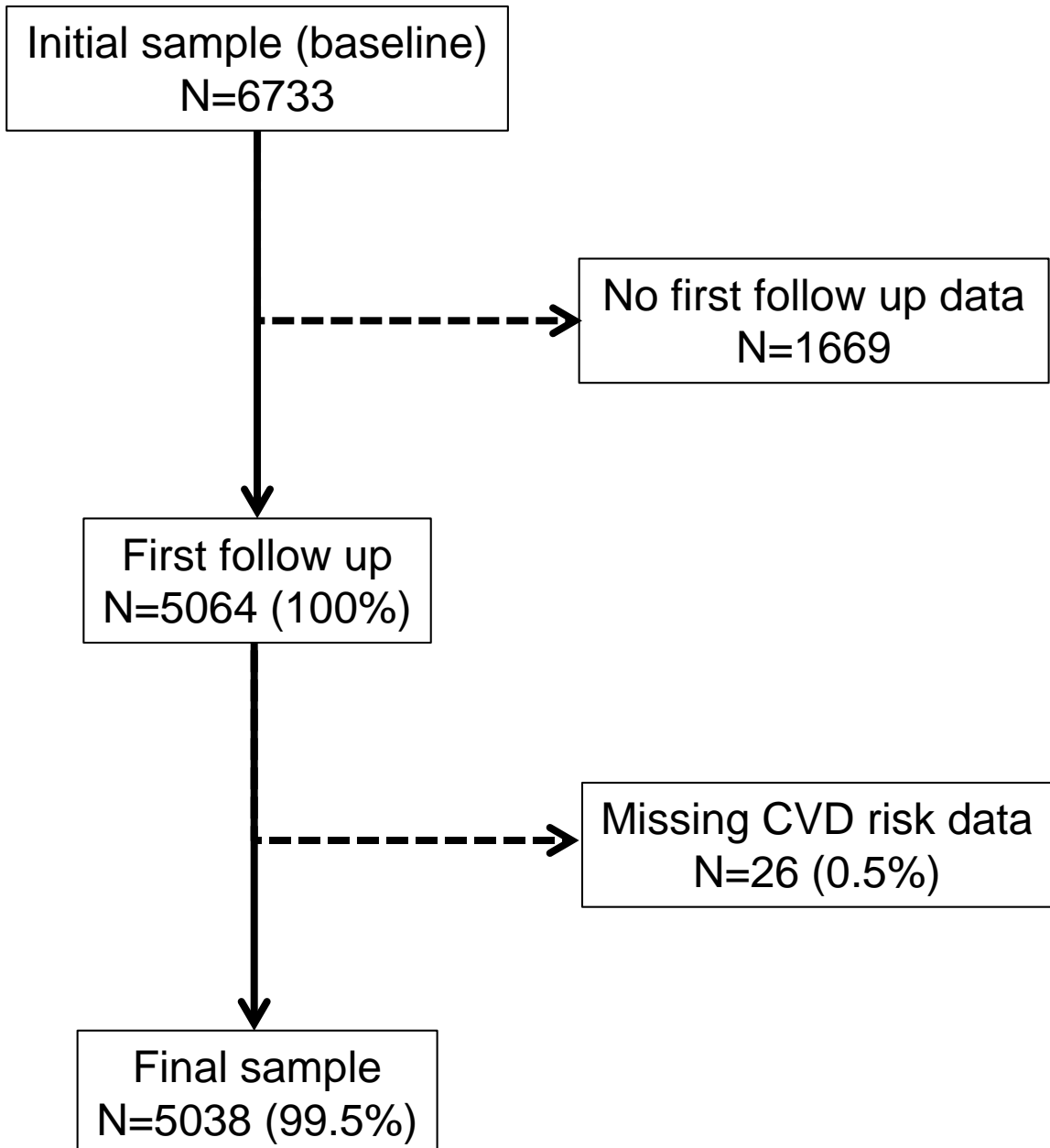


Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

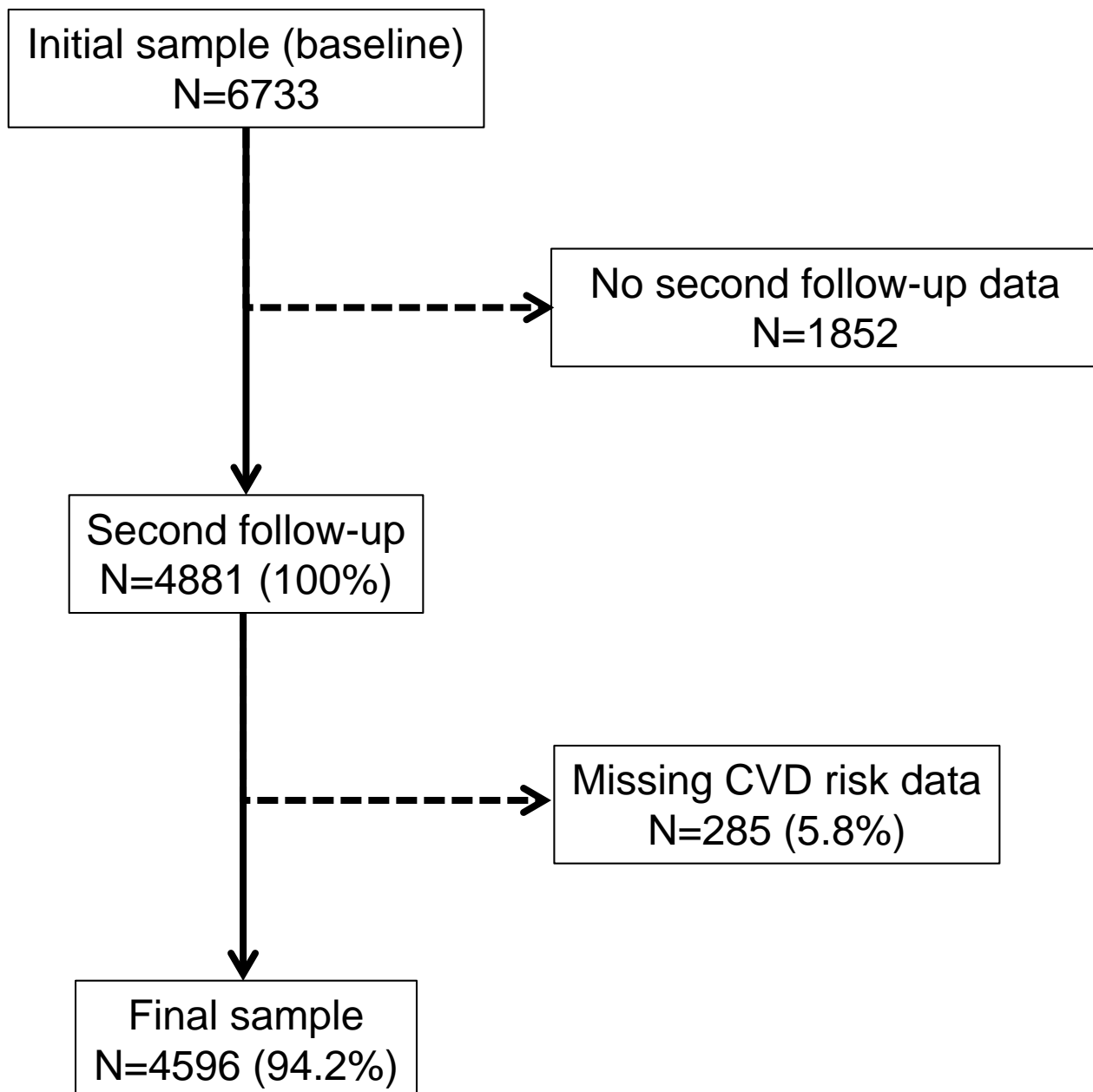
© The Author(s) 2021

Supplementary figure 1: Data selection procedure

Panel A: First follow-up



Panel B: Second follow-up



POLYPILL ELIGIBILITY AND EQUIVALENT INTAKE IN A SWISS POPULATION-BASED STUDY

Julien Castioni*, MD; Nazanin Abolhassani*, PhD; Peter Vollenweider; Gérard Waeber, MD; Pedro Marques-Vidal, MD, PhD.

Department of Medicine, Internal Medicine, Lausanne university hospital and University of Lausanne,
Lausanne, Switzerland

* These authors contributed equally

Authors' emails:

Julien Castioni: Julien.Castioni@chuv.ch
Nazanin Abolhassani: Nazanin.abolhassani@chuv.ch
Peter Vollenweider: Peter.Vollenweider@chuv.ch
Gérard Waeber: Gerard.Waeber@chuv.ch
Pedro Marques-Vidal: Pedro-Manuel.Marques-Vidal@chuv.ch

Authors' ORCID

Julien Castioni: 0000-0002-7260-9371
Nazanin Abolhassani: 0000-0002-3616-3595
Peter Vollenweider: 0000-0002-0765-896X
Gérard Waeber: 0000-0003-4193-788X
Pedro Marques-Vidal: 0000-0002-4548-8500

Address for correspondence and reprints

Nazanin Abolhassani
Room BH10-636
Department of Medicine, Internal Medicine
Lausanne university hospital
Rue du Bugnon 46
1011 Lausanne
Switzerland
Phone: +41 21 314 09 82
Email: Nazanin.abolhassani@chuv.ch

SUPPLEMENTAL TABLES

Supplemental table 1: characteristics of included and excluded participants, Colaus study, Lausanne, Switzerland, 2009-2012 and 2014-2017.

	First follow-up (2009-2012) (N=5064)			Second follow-up (2014-2017) (N=4881)		
	Included	Excluded	P-value	Included	Excluded	P-value
All	5038 (99.5)	26 (0.5)		4596 (94.2)	285 (5.8)	
Gender			0.968			0.462
Woman	2693 (53.5)	14 (53.8)		2526 (55.0)	163 (57.2)	
Man	2345 (46.5)	12 (46.2)		2070 (45.0)	122 (42.8)	
Age group			0.653			0.002
[40-50[1421 (28.2)	10 (38.5)		561 (12.2)	19 (6.7)	
[50-60[1533 (30.4)	7 (26.9)		1474 (32.1)	96 (33.7)	
[60-70[1348 (26.8)	5 (19.2)		1222 (26.6)	99 (34.7)	
[70+	736 (14.6)	4 (15.4)		1339 (29.1)	71 (24.9)	
Smoking status			0.813			0.001
Never	2025 (40.7)	10 (38.5)		1781 (41.7)	105 (46.9)	
Former	1874 (37.6)	9 (34.6)		1692 (39.6)	62 (27.7)	
Current	1082 (21.7)	7 (26.9)		798 (18.7)	57 (25.4)	
History of CVD			0.422 §			<0.001 §
No	4873 (96.7)	26 (100.0)		4252 (92.5)	285 (100.0)	
Yes	165 (3.3)	0 (0.0)		344 (7.5)	0 (0.0)	

Results are expressed as number (percentage). Between-group comparisons performed using chi-square or Fisher's exact test (§).

Supplemental table 2: Prevalence of polypill eligibility and any polypill equivalents intake, Colaus study, Lausanne, Switzerland, 2009-2012 and 2014-2017.

	Eligible, 2009-2012		Eligible, 2014-2017	
Any polypill equivalent intake	No	Yes	No	Yes
No	3120	887	3763	733
Yes	201	388	236	306

Supplemental table 3: Drugs prescribed, ColaUS study, Lausanne, Switzerland, 2009-2012 and 2014-2017.

Prescribed Drugs	2009-2012 (N=5038)	2014-2017 (N=4596)
Antiplatelet drugs		
Any	585 (11.6)	699 (12.8)
Aspirin	559 (11.1)	655 (14.3)
Hypolipidaemic drug treatment		
Any	932 (18.5)	936 (20.4)
Statins	880 (17.5)	876 (19.1)
Other hypolipidemic drugs	79 (1.6)	91 (2.0)
Antihypertensive drug treatment		
Any	1352 (26.3)	1525 (33.2)
Angiotensin receptor blockers	654 (13.0)	765 (16.6)
ACE inhibitors	358 (7.1)	408 (8.9)
Beta-blockers	452 (9.0)	525 (11.4)
Calcium channel blockers	271 (5.4)	328 (7.1)
Diuretics	405 (8.0)	491 (10.7)
Hydrochlorothiazide	259 (5.1)	333 (7.3)
Other antihypertensive drugs §	18 (0.4)	25 (0.5)

Results are expressed as number of participants (percentage). § peripheral vasodilators or post-synaptic stimulators.