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Journal

Journal of Clinical Pharmacy and Therapeutics, 42(2)

ISSN

0269-4727

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Publication Date

2017-04-01

DOI

10.1111/jcpt.12502

Peer reviewed

HHS Public Access

Author manuscript

J Clin Pharm Ther. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

J Clin Pharm Ther. 2017 April ; 42(2): 228–233. doi:10.1111/jcpt.12502.

Potential Drug-Drug and Drug-Disease Interactions in Well Functioning Community Dwelling Older Adults

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Abstract

What is Known and Objective—There are few studies examining both drug-drug and drug-disease interactions in older adults. Therefore the objective of this study was to describe the prevalence of potential drug-drug and drug-disease interactions and associated factors in community dwelling older adults.

Methods—This cross-sectional study included 3055 adults aged 70–79 without mobility limitations at their baseline visit in the Health Aging and Body Composition Study conducted in the communities of Pittsburgh PA and Memphis TN, USA. The outcome factors were potential drug-drug and drug-disease interactions as per the application of explicit criteria drawn from a number of sources to self-reported prescription and nonprescription medication use.

Results—Over 1/3 of participants had at least one type of interaction. Approximately one quarter (25.1%) had evidence of had one or more drug-drug interactions. Nearly 10.7% of the participants had a drug-drug interaction that involved a nonprescription medication. % The most common drug-drug interaction was nonsteroidal antiinflammatory drugs (NSAIDs) affecting antihypertensives. Additionally, 16.0% had a potential drug-disease interaction with 3.7% participants having one involving nonprescription medications. The most common drug-disease

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Conflict Of Interest:
No conflicts of interest have been declared

interaction was aspirin/NSAID use in those with history of peptic ulcer disease without gastroprotection. Over 1/3 (34.0%) had at least one type of drug interaction. Each prescription medication increased the odds of having at least one type of drug interaction by 35–40% (drug-drug interaction-adjusted odds ratio[AOR]=1.35, 95% confidence interval[CI]=1.27–1.42; drug-disease interaction- AOR=1.30; CI=1.21–1.40; and both AOR=1.45; CI=1.34–1.57). A prior hospitalization increased the odds of having at least one type of drug interaction by 49–84% compared to those not hospitalized (drug-drug interaction-AOR=1.49, 95% CI=1.11–2.01; drug-disease interaction-AOR=1.69, CI=1.15–2.49; and both AOR=1.84, CI=1.20–2.84).

What is New and Conclusion—Drug interactions are common among community dwelling older adults and are associated with the number of medications and hospitalization in the previous year. Longitudinal studies are needed to evaluate the impact of drug interactions on health-related outcomes.

Keywords

Aged; drug interaction; drug utilization

What is Known and Objective

While the benefits of medication therapy for older adults to treat disease and improve or maintain quality of life are substantial, they must be balanced by their risks. One such risk is potentially inappropriate medication (PIM) use which can be defined as prescribing/use that does not agree with accepted medical standards.[1–3] Two important specific types of PIM in older adults are drug-drug and drug-disease interactions which increase the risk of adverse drug reactions (ADRs), functional status decline, health services use and mortality in older adults.[2–8]

Although various explicit criteria to define drug-drug and drug-disease interactions were available more than two decades ago, they rarely have both been applied to self-reported use of both prescription and non-prescription medications in well-functioning community-dwelling older adults.[2] Even less is known about factors associated with these two types of PIM. This is an important gap in knowledge to be filled so health professionals can a priori better identify those individuals at risk and initiate appropriate preventative measures. Therefore, the study objective was to describe the prevalence of and factors associated with both drug-drug and drug-disease interactions with prescription and non-prescription medications among community dwelling older adults.

Methods

Study Design, Data Source and Sample

This cross-sectional study used data collected from 3,075 black and white men and women aged 70–79 enrolled in the baseline survey of the Health, Aging and Body Composition (Health ABC) study.[9] Participants were recruited from Pittsburgh and Memphis. To be included, they had to report no difficulty walking at least 1/4 mile or up a flight of stairs. Trained research assistants collected detailed physiologic measurements (e.g., height, weight) and fasting blood samples (e.g., fasting glucose, serum creatinine) during the

baseline in-clinic visit. Blood samples were frozen and sent for storage in a central laboratory repository where batch testing was conducted. Other information collected by questionnaire included demographics, and health behavior/ status factors and physiological and access to care factors. Regarding data collection for medication use, participants were asked to bring to clinic all medications they had taken in the previous month. In clinic, the interviewer gathered all prescription and non-prescription drugs and transcribed from the medication container information about the drug name, strength, dosage form, and prescription or non-prescription status. The medication data collected for the Health ABC study was edited and then coded using the Iowa Drug Information System (IDIS) ingredient codes by entry into a computerized database.[10] Twenty participants did not provide medication use information and were excluded from the final sample. Thus the final sample for these analyses was 3055 participants.[11]

Outcome Factors

Potential clinically important drug-drug interactions were detected at baseline by applying explicit criteria for 70 potential drug-drug interactions developed by panels of geriatric experts and/or were found to be a common cause of drug-related hospitalization in the literature prior to the start of this study (Table 2).[4–6, 11–14] Specifically, 13 are from the 2015 update of the American Geriatrics Society Beers criteria.[11] otential drug-drug interactions were also characterized by their mechanism (i.e., pharmacokinetic [PK] if they involved the alteration in the absorption, distribution, metabolism or excretion of the affected drug [e.g., verapamil interacting with digoxin] versus pharmacodynamic [PD] if they involved an alteration in the biochemical and physiological effects of the affected drug on the body [e.g., the use of two separate highly anticholinergic medications]). Similarly, 30 of 32 potential clinically important drug-disease interactions (e.g., non-steroidal antiinflammatory drugs[NSAIDs] and heart failure) were detected by applying explicit criteria from the 2015 update of the American Geriatrics Society Beers criteria with the remaining two developed by panels of geriatric experts and/or were found to be a common cause of drug-related hospitalization in the literature prior to the start of this study (Table 3).[4–6, 12–14] Valid and reliable self-reported physician diagnosed disease/conditions assessed for drug interactions included chronic constipation, falls/fracture history, heart failure, peptic ulcer disease, syncope history, benign prostatic hypertrophy symptoms in men, urinary incontinence in females, Parkinson’s disease and seizure disorder.[9] Cognitive impairment was defined as scoring less than 80 on the Modified Mini Mental State exam.[9] We used serum creatinine values, gender and weight to calculate estimated creatinine clearance (eCrClr) to identify participants with stage 3 chronic kidney disease (CKD) (i.e., CrClr<30ml/min) using the following Cockcroft- Gault equation.[9]

Independent Variables

Based on previous literature, the independent variables included demographics, health behavior/status factors, and access to care factors.[15–17] Demographics included dichotomous variables for race, sex, site (i.e., Pittsburgh, PA or Memphis, TN where data were collected), education, and marital status. We also included a dichotomous and continuous measure for age.

Health behavior/status categorical variables included current smoking and alcohol use. In addition, dichotomous health status variables included self-reported arthritis, anxiety and severe depressive symptoms (measured by modified short CES-D, score>10), bodily pain in the previous month, and self-rated health (excellent/very good/ good vs fair/poor).[18–21] Participants were identified as having diabetes mellitus by using an American Diabetes Association validated approach in which they self-reported that a physician told them they had diabetes or sugar diabetes, had current use of one or more antidiabetic medications (e.g., insulin, sulfonylureas, biguanides), or had a fasting glucose ≥ 126 mg/dl.[9] A categorical variable was included for body mass index (under/normal [<24.9], overweight [25.0–29.9], obese [30+]). We also included a continuous variable for number of prescription medications to serve as a proxy comorbidity measure. Finally, we included dichotomous access to care variables for hospitalization in previous year, having a prescription drug benefit, having a private physician, and whether the participant received an influenza vaccination in the previous year as a proxy for quality of care.[22]

Analyses

Descriptive statistics were used to summarize independent variables and drug-drug and drug-disease interaction variables. We used multinomial logistic regression models with 4-level categorical outcome of drug interaction type (none/drug-drug/drug-disease/both) as the dependent variable; generalized logit link function; each of the demographic, health behavior/status and access-to-care factors as independent variables; person as the unit of analysis; and stepwise selection approach with an α=0.05 criterion for entry into the model to identify a parsimonious set of factors independently associated with drug interactions.[23] Race, sex, age, site, education, marital status, arthritis, depression and bodily pain were forced in based on a priori perception of likely association. We report adjusted odds ratios and 95% confidence intervals from the final model. Because the confidence intervals and commonly reported p-values are specific to the odds ratios reported, we additionally computed type 3 p-values to examine the significance of overall association between an independent variable and multinomial dependent variable while simultaneously considering multiple odds ratios. Briefly, a type 3 p-value is computed by comparing two statistical models fitted with and without the categorical variable, rather than one model as commonly done. Statistical analyses were performed using SAS® (version 9.3; SAS Institute, Inc., Cary, NC).

Ethical approval

This study was approved by the University of Pittsburgh Institutional Review Board.

Results

Demographics, health status and access to care factors

Table 1 shows the baseline characteristics of the sample. Overall, 62.7% were less than 75 years of age, slightly more than half were female, and 83.7% rated their health as excellent/ very good or good. Only 9.2% took 5 or more drugs.

Prevalence of drug-drug and drug disease interactions

Over 1/3 of participants had at least one type of drug interaction. Approximately one quarter (25.1%) had evidence of one or more potential drug-drug interactions. Nearly 10.7% of all participants had a drug-drug interaction that involved a nonprescription medication. Table 2 shows the number of drug-drug interactions grouped by major therapeutic classes. The most common major therapeutic class affected by other drugs was cardiovascular medications. The most common drug class affecting other drugs was NSAIDs. The underlying mechanism involved in the majority of drug-drug interactions was pharmacodynamic in nature. Only 66 (2.16%) had a potential drug-drug interaction involving narrow therapeutic range drugs (i.e., digoxin, lithium, phenytoin, theophylline, warfarin).

Drug-disease interactions occurred in 16.0% of all participants, with 3.7% of all participants having one involving non-prescription medications. Table 3 shows that the most common drug-disease interactions (in both sexes) involved those with a history of peptic ulcer disease and taking aspirin/NSAIDs without gastroprotection, or having a history of falls/fractures in those taking one of five CNS medication classes. No drug-disease interactions were detected for those with Parkinson's disease (all antipsychotics [except aripiprazole, quetiapine and clozapine], metoclopramimde, prochlorperazine, promethazine or those with a seizure disorder (bupropion, chlorpromazine, clozapine, maprotiline, olanzapine, thioridazine, thiothixene, tramadol).

Factors associated with drug-interactions

Table 4 shows the multivariable associations of factors with having only a potential drug-drug interaction, only a drug-disease interaction, or both a drug-drug and drug-disease interaction. When combined, 34.0% of individuals had one or more potential drug-drug or drug-disease interactions with 38.2% of these involving a non-prescription medication. Each prescription medication increased the odds of having at least one type of drug interaction by 35–40% (drug-drug interaction-adjusted odds ratio [AOR]=1.35, 95% confidence interval [CI]=1.27–1.42; drug-disease interaction-AOR=1.30, CI=1.21–1.40; and both-AOR=1.45; CI=1.34–1.57). A prior hospitalization increased the odds of having at least one type of drug interaction by 49–84% compared to those not hospitalized (drug-drug interaction-AOR=1.49, 95% CI=1.11–2.01; drug-disease interaction-AOR=1.69, CI=1.15–2.49; and both-AOR=1.84, CI=1.20–2.84). Those with arthritis were more likely to have either a drug-drug interaction (AOR=1.80; CI=1.42–2.27) only or both types (AOR=2.85; CI=1.83–4.41) while those with excellent/very good self-reported health were less likely to have the same (AORs=0.61 and 0.43; CIs=0.45–0.82 and 0.28–0.66, respectively). Those with anxiety symptoms were more likely to have either a drug-disease interaction only or both types (AOR=1.55 and 1.68; CI=1.05–2.27 and 1.06–2.66, respectively) whereas other demographic (age, marital status), and health status factors (diabetes, bodily pain, higher body mass index) were associated with one of the three drug interaction categories as shown in Table 4.

What Is New and Conclusion

Principal findings and comparison with previous literature

Slightly more than 1/3 of well-functioning community-resident adults aged 70 to 79 years had a potential drug interaction. . In contrast, Hanlon et al., had found that only 13.2% of community dwelling elders had one or more of these two PIM types in an analysis that was restricted to those involving only 8 therapeutic drug classes that included both prescription and non-prescription medications.[24] The difference between these two rates may be due to the sample from the Hanlon et al study being younger than those from the current study. Other studies to date generally examined only one of the two PIM types, did not consider the overall prevalence of any type of drug interaction and/or did not include non-prescription medications.[1–3, 15–17] Nonetheless, some previous studies linked drug interactions with increased risk of ADRs in older adults or causing the ADR.[4–8] Moreover, one study showed that older adults with either type of drug interaction had an increased risk of decline in performing basic activities of daily living.[24]

Only two factors were associated with drug interactions (i.e., number of medications and history of hospitalization in the previous year). The finding that number of drugs was a risk factor is not surprising and was also found in a study examining the risk of drug-disease interactions in older outpatient veterans and it serves as a proxy measure of comorbidity.[15] A possible explanation for prior hospitalization being a risk factor is that it may serve as a proxy for overall disease burden in older adults.[25] These two factors and other demographics and health status factors may be useful in targeting specific segments of older adults for pharmacy intervention.

It is interesting to note that NSAIDs (including aspirin) were the most common drug class involved with both types of drug interactions. This is important as daily NSAID use is common in older adults. A recent study by our group using Health ABC data documented that more than one in ten participants used daily NSAIDs and over a quarter of this use was due to non-prescription NSAID products.[26] Pharmacists should be cognizant that NSAIDs use is generally not recommended first line for management of chronic non-cancer pain due in part to their potential to increase the risk of peptic ulcer disease especially in those with a previous history or in those using other drugs that can cause peptic ulcer disease (i.e. corticosteroid, antiplatelets).[27] In older adults where NSAID use is necessary, gastroprotection with a proton pump inhibitor is recommended.[26] Unfortunately, gastroprotection is underused even in those with a drug benefit.[26]

Strengths and Limitations

The strengths of the study include the community based sample of well-functioning elders. Moreover, state of the art methods were used to collect and numerically code the medication data that included non-prescription products. In addition, we were able to detect both drug-drug interactions with pharmacodynamic mechanisms and drug-disease interactions that can’t be screened with using only computerized pharmacy dispensing data. As with any study, several limitations should be considered. First, because of the cross sectional design we cannot be specific as to the exact chronological order between our dependent and

independent variables. Second, the rate of drug interactions observed in this study may be conservative given that our sample did not have mobility problems, CKD or heart failure. Finally, the extent of generalizability to the entire US older population is not known.

Implications for practice and future research

Our study found that a large number of drug interactions involved non- prescription medications. This point reinforces the need for pharmacist to carefully query older adults about their use of non-prescription medications when taking a medication history. In addition only two factors were associated with drug-interactions. This may allow pharmacist to prioritize screening those with multiple medications or polypharmacy and those recently discharged from the hospital for providing medication therapy management services for older adults.

In conclusion, drug interactions are common among non-frail community dwelling older adults and associated with the number of medications and a hospitalization during the prior year. Longitudinal studies in older adults are needed to examine the impact of these drug interactions on health-related outcomes such as functional status, health services use and mortality.

Acknowledgments

The authors would like to thank Ken Kang, PhD for his assistance with some of the data analyses and Robert Boudreau, PhD for sharing his expertise about using Health ABC study data.

Funding Support:

The research reported in this manuscript was primarily supported by National Institute on Aging (NIA) grants and contracts (P30-AG024827, T32-AG021885). This research was also supported in part by the Intramural Research program of the NIH, NIA (N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106), NIA grant (R01-AG028050), and a National Institute of Nursing Research grant (R01-NR012459).

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Table 1

Characteristics of the Participants (n=3055)

Variables	n, %	Mean +/− (SD)
Demographics		
Black race	1266 (41.4)	
Female sex	1574 (51.5)	
Age (< 75 years)	1916 (62.7)	73.6 (2.9)
Site (Pittsburgh)	1516 (49.6)	
High school graduate	1285 (42.0)	
Married	1568 (51.3)	
Health Behaviors/Status		
Current smoker	316 (10.3)	
Alcohol use (≥1 drink per week)	874 (28.6)	
Arthritis	1709 (55.9)	
Diabetes	467 (15.3)	
Anxiety symptoms	430 (14.1)	
Depressive symptoms (Short CES-D>10)	176 (5.8)	
Bodily pain (any in past month)	1999 (65.4)	
Self-rated health (excellent/very good/good)	2558 (83.7)	
Health Status/Behaviors		
Body mass index		
Underweight/Normal (<24.9)	982 (32.1)	
Overweight (25.0–29.9)	1293 (42.3)	
Obese (30+)	780 (25.5)	
Prescription medications		1.73 (2.0)
Access to Care		
Hospitalization (any in previous year)	457 (15.0)	
Prescription drug benefit	1925 (63.0)	
Private physician	2388 (78.2)	
Influenza vaccination in previous year	2103 (68.8)	

Table 2

Prevalence of Potential Drug-Drug Interactions by Therapeutic Drug Class and Individual Agents (n=3055)[a]

Drug Class/Medication Affected	Drug/Class Interacting	Mechanism	N (%)
Antithrombotics			**266 (8.7)**
Antiplatelet agents including aspirin	NSAID	PD	231
Warfarin	Antiplatelet agents including aspirin	PD	4
Warfarin	Amiodarone	PK	1
Warfarin	Cimetidine	PK	1
Warfarin	NSAID	PD	29
Cardiovascular			**739 (24.2)**
ACE-I	Potassium supplement	PD	61
ACE-I	Potassium sparing diuretics	PD	30
Antihypertensive	Levodopa	PD	8
Antihypertensive	NSAID	PD	419
ARB	Potassium supplement	PD	8
ARB	Potassium sparing diuretics	PD	3
Calcium channel blocker	Nitrates	PD	93
Digoxin	Amiodarone	PK	1
Digoxin	Verapamil	PK	17
Digoxin	Propafenone	PK	3
Digoxin	Quinidine	PK	7
Diuretics, loop & thiazide	Nitrates	PD	64
Potassium sparing diuretics	Potassium	PD	25
Central Nervous System			**54 (1.8)**
ACHEI	Anticholinergic	PD	2
Antidepressant	Antipsychotic	PD	15
Antidepressant	BZD agonist	PD	29
Antipsychotic	BZD agonist	PD	4
Lithium	NSAID	PK	1
Phenytoin	Omeprazole	PK	1
SSRI	Other serotonergic drugs	PD	2
ENDOCRINE			**75 (2.)**
Corticosteroids, oral	NSAIDs	PD	16
Statins metabolized by CYP3A4 (atorvastatin, lovastatin, simvastatin)	Diltiazem	PK	34
Statins metabolized by CYP3A4 (atorvastatin, lovastatin, simvastatin)	Verapamil	PK	17
Statins, all	Gemfibrozil	PK	6

Drug Class/Medication Affected	Drug/Class Interacting	Mechanism	N (%)
Tamoxifen	Paroxetine	PK	2
MISCELLANEOUS			**1**
Theophylline	Cimetidine	PK	1

[a]Participants could have >1 potentially inappropriate drug-drug interaction.

Abbreviations: ACE-I=angiotensin converting enzyme inhibitor, ACHEI=acetylcholinesterase inhibitor, ARB=angiotensin receptor blocker, BZD=benzodiazepine, NSAID=nonsteroidal anti-inflammatory drug, PD=pharmacodynamic, PK=pharmacokinetic, SSRI=selective serotonin reuptake inhibitor

Table 3

Specific Medications Involved in Potential Drug-Disease Interactions (n=3055)[a]

Potential Drug-Disease Interaction	N (%)
Chronic kidney disease	**8 (0.3)**
NSAID	6
Triamterene	3
Cognitive impairment	**71 (2.3)**
Anticholinergics	33
BZD receptor agonists	17
Histamine$_2$ blockers	39
Constipation, chronic	**18 (0.6)**
Anticholinergics	13
Diltiazem/verapamil	9
Falls/fracture history	**121 (4.0)**
Anticonvulsants	27
Antipsychotics	8
BZD receptor agonists	62
SSRIs	31
TCAs	21
Heart failure	**19 (0.6)**
Diltiazem/Verapamil	4
NSAIDs	15
BPH in men	**22 (0.7)**
Anticholinergics	27
PUD (unless receiving gastroprotection)	**130 (4.3)**
Aspirin >325mg/day	180
Non COX-2 selective NSAID	125
Sleep problems	**46 (1.5)**
Sympathomimetics (e.g., pseudoephedrine)	31
Theobromines (e.g., theophylline)	19
Syncope history	**20 (0.7)**
ACHEI	1
Alpha blockers, peripheral	16
Antipsychotics	1
Tertiary TCA	2
Urinary problem in females	**119 (3.9)**
Alpha blockers, peripheral	14
Estrogen	114

[a]Participants could have >1 potentially inappropriate medication for one disease state.

Abbreviations: ACHEI=acetylcholinesterase inhibitor, BZD=benzodiazepine, BPH=Benign prostatic hypertrophy, NSAID=nonsteroidal anti-inflammatory drug, PUD=peptic ulcer disease, SSRI=selective serotonin reuptake inhibitor, TCA=tricyclic antidepressant.

Table 4

Multivariable Factors Associated with Potential Drug-Drug Interaction Only (n=551), Drug-Disease Interaction Only (n=272) and Both (n=216) Compared to Those with No Interactions (n=2016)

Variables	Drug-Drug Interaction Only[b] (N=551)	Drug-Disease Interaction Only[b] (N=272)	Both Drug-Drug & Drug-Disease Interactions[b] (N=216)
	Adj. Odd Ratio (95%CI)	Adj. Odd Ratio (95%CI)	Adj. Odd Ratio (95%CI)
Black race	0.85 (0.66–1.10)	1.81 (1.25–2.62)	1.03 (0.67–1.57)
Female sex	0.88 (0.69–1.12)	**0.45 (0.32–0.63)**	**0.50 (0.33–0.75)**
Age <75	1.13 (0.90–1.41)	0.74 (0.54–1.00)	**0.68 (0.47–0.99)**
Site (Pittsburgh)[a]	**1.27 (1.02–1.58)**	1.25 (0.93–1.70)	1.41 (0.98–2.03)
High school graduate[a]	0.94 (0.71–1.24)	0.85 (0.59–1.24)	0.89 (0.58–1.37)
Married	**1.32 (1.03–1.68)**	0.74 (0.54–1.02)	1.15 (0.78–1.70)
Health Status/Behaviors	--	--	--
Arthritis	1.80 (1.42–2.27)	0.95 (0.70–1.30)	**2.85 (1.83–4.41)**
Diabetes	0.74 (0.54–1.00)	**0.60 (0.38–0.95)**	0.62 (0.38–1.03)
Anxiety symptoms	1.06 (0.76–1.47)	**1.55 (1.05–2.27)**	**1.68 (1.06–2.66)**
Bodily pain[a]	**1.31 (1.02–1.67)**	1.25 (0.89–1.76)	0.84 (0.55–1.27)
Depressive symptoms[a] (Short CES-D>10)	0.73 (0.42–1.26)	1.26 (0.72–2.18)	1.30 (0.67–2.49)
Self-rated Health (Excellent/very good/good)	**0.61 (0.45–0.82)**	0.75 (0.50–1.12)	**0.43 (0.28–0.66)**
Body Mass Index			
Underweight/normal	reference	reference	reference
Overweight	**1.39 (1.06–1.82)**	1.10 (0.78–1.55)	1.35 (0.87–2.10)
Obese	**2.09 (1.56–2.81)**	0.99 (0.66–1.49)	1.43 (0.87–2.33)
Number of prescription medications	**1.35 (1.27–1.42)**	**1.30 (1.21–1.40)**	**1.45 (1.34–1.57)**
Access to Care			
Hospitalization in previous year	**1.49 (1.11–2.01)**	**1.69 (1.15–2.49)**	**1.84 (1.20–2.84)**
Private physician	**1.36 (1.01–1.81)**	**0.67 (0.47–0.95)**	1.23 0.78–1.93)

[a] Type 3 p-value>0.05

[b] Bolded numbers are p<0.05