Management of Severe Multimorbidity (SMM) in the midst of cognitive decline, using an AI precision-medicine platform

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Background

Multimorbidity is the presence of two or more chronic conditions at the same time, with severe multimorbidity (abbreviated here as SMM) indicating three or more. Chronic conditions fall into different domains (*e.g.*, cardiovascular or endocrine), and many of the conditions themselves, such as diabetes, contribute to the onset and progression of cognitive decline. Chronic conditions may interact, curtailing compensatory mechanisms and increasing the likelihood of both physical and cognitive decline. Physicians often mis-diagnose cognitive decline when addressing SMM, while cognitive decline, in turn, can reduce a person's ability to manage SMM. This becomes a vicious cycle.

uMETHOD Health has developed an AI precision-medicine platform for addressing cognitive decline (that is, dementia, MCI, and mild AD)[1]. The software implements the multidomain principles seen in the FINGER study[2], the Weill-Cornell Alzheimer's Prevention Clinic (APC)[3], and the 2017 & 2020 Lancet Reports[4,5]. It creates tailored treatment plans for use in doctors' practices. Incoming data includes genomics, problem list and medical history, current medications, and results from biospecimen and cognitive testing. The computer-generated care plans personalize recommendations on lifestyle changes, medications, and follow-on diagnostics.

Materials and Methods

The algorithms in this AI platform compare an individual's status among multiple physiological and lifestyle states known to be contributors to cognitive decline against desired normative states. Drivers of MCI and Alzheimer's disease are evaluated, weighted, and prioritized. The output is a personalized, multidomain treatment plan designed for use by physicians in the care of their patients.

Two populations were evaluated in this assessment. Each person in these populations was evaluated with the same platform, thus identically processing their demographics, biospecimen results, vitals, medication lists, cognitive assessments, and comorbidity lists.

1) 3,876 individuals 65 years or older (2,261 females, 1,615 males) who have received uMETHOD care plans, that is, they are being treated for the prevention or presence of cognitive decline.
2) 88,824 individuals age 0 to 79 (44,950 females, 43,874 males) across the 10 volumes of datasets in The National Health and Nutrition Examination Survey (NHANES)[6], covering 1999 to 2018. NHANES includes individuals 85 and older, but early volumes reported ages of those 85 and older as simply 85, and later volumes lowered this upper bound to 80. This artificially increased the number of individuals age 80 or 85, so the population was limited to those 0 to 79. Many comorbidities can be determined from an individual's medications and a set of ad-hoc questions, but it is not a complete list of comorbidities for that person. Of these 88,824 people, only 146 were diagnosed with cognitive decline, which is not representative of the general population. As such, this large dataset is only used in analyses that do not involve cognitive decline.

The 3,876 people in the uMETHOD dataset were identified as having cognitive decline if their physicians' diagnoses included MCI, Alzheimer's disease, or dementia, or if their medications include a drug used for the treatment of those conditions. Using these criteria, 1,912 individuals (49.3%) were identified with cognitive decline.

Having an accurate list of chronic conditions is essential to the results reported below. There are a variety of inherent reasons why a problem list may not be accurate: out-of-date medical history, omissions in the medical history, undiagnosed conditions, and transcription errors. The AI platform compensates for this by examining biospecimen results, vitals, medication lists, and genomic information to determine the likelihood of over 50 chronic conditions. It weighs these accordingly in its analysis of the factors driving cognitive decline.

Pearson's correlation coefficient was used to determine which chronic conditions have statistically significant, positive linear correlations with cognitive decline. These conditions, whether provided in a problem list or observed by the AI platform, were used as the factors in determining multimorbidity.

Table 1 shows the conditions with a statistically significant, positive linear correlation with cognitive decline. "r" is Pearson's correlation coefficient, a measure of the linear correlation between two sets of variables, normalized such that the value is always between -1 and 1. P-value evaluates how well the data rejects the "null hypothesis", which states that there is no relationship between the two sets of variables. A p-value of 0.05 or less is considered statistically significant.

Condition	r	p-value
heart disease	0.249	<0.0001
poor sleep quality	0.200	<0.0001
osteoarthritis	0.170	<0.0001
hypothyroidism	0.168	<0.0001
GERD	0.159	<0.0001
lipid disorders	0.159	<0.0001
depression	0.141	<0.0001
metabolic acidosis	0.124	<0.0001
stroke	0.108	<0.0001
chronic lung disease	0.102	<0.0001
atrial fibrillation	0.101	<0.0001
cancer	0.100	<0.0001
chronic kidney disease	0.091	<0.0001
hypertension	0.073	<0.0001
liver disease	0.052	0.0010
Parkinson's disease	0.041	0.0098
diabetes type 2	0.033	0.0317

Table 1 shows the chronic conditions with a statistically significant, positive linear correlation with cognitive decline.

In addition to the chronic conditions in Table 1, six additional chronic condition are included here, as multiple studies have demonstrated statistically significant, positive linear correlations with cognitive decline:

- hyponatremia[17-18]
- monocytopenia[16]
- thrombocytopenia
- obesity
- metabolic syndrome[13-15]
- achlorhydria

Results

Table 2 shows the frequency of the chronic conditions that determine multimorbidity. "n" is the number of individuals with that chronic condition, whether that condition was explicitly reported in a medical history or observed by the AI platform. In Table 2 below, the NHANES dataset was limited to individuals aged 65 – 79 (9,638 individuals, 4,772 female, 4866 male) for comparison with the uMETHOD dataset. The NHANES dataset does not provide enough information for the AI platform to determine the likelihood of metabolic acidosis.

Condition	uMETHOD		NHANES (65-79)	
	n	% of Population	n	% of Population
lipid disorders	2,718	70.1%	6,003	62.3%
hypertension	2,575	66.4%	4,639	48.1%
chronic kidney disease	2,276	58.7%	2,508	26.0%
depression	1,420	36.6%	1,054	10.9%
obesity	1,164	30.0%	3,426	35.5%
diabetes type 2	941	24.3%	2,644	27.4%
GERD	887	22.9%	663	6.9%
heart disease	835	21.5%	189	2.0%
poor sleep quality	801	20.7%	256	2.7%
hypothyroidism	744	19.2%	300	3.1%
osteoarthritis	741	19.1%	83	0.9%
metabolic syndrome	726	18.7%	2,551	26.5%
chronic lung disease	527	13.6%	159	1.6%
metabolic acidosis	372	9.6%	N/A	N/A
atrial fibrillation	322	8.3%	294	3.1%
cancer	265	6.9%	2,028	21.0%
thrombocytopenia	199	5.1%	335	3.5%
liver disease	198	5.1%	21	0.2%
hyponatremia	162	4.2%	308	3.2%
stroke	156	4.0%	31	0.3%
achlorhydria	149	3.8%	186	1.9%
Parkinson's disease	75	1.9%	56	0.6%
monocytopenia	8	0.2%	1	0.01%

Table 2 shows the frequency of the conditions reported in medical histories or observed by the AI platform.

Table 3 illustrates how the AI platform can improve the accuracy of assessing the chronic conditions that an individual might have. In Table 3:

- "n" is the number of individuals in a dataset with the condition
- "Reported" is the number of individuals with the condition, where the medical history explicitly mentions the condition
- "Observed Only" is the number of individuals with the condition that were not explicitly noted in the medical history, but were observed by the AI platform from biomarkers and vitals
- "Med Only" is the number of individuals with the condition that were not explicitly noted in the medical history, but were inferred by the AI platform from the medications for the individual
- "--" in a cell indicates a feature not currently implemented in the AI platform
- "N/A" indicates that the NHANES dataset does not provide enough information for the AI platform to determine the likelihood of metabolic acidosis.

Condition	uMETHOD				NHANES (0-79)			
	n	Reported	Observed Only	Med Only	n	Reported	Observed Only	Med Only
lipid disorders	2,718	1,892	119	694	23,870	2,963	16,842	2,678
hypertension	2,575	1,714	10	851	10,557	4,523	0	6,034
CKD	2,276	393	1,883	--	3,441	61	3,380	--
depression	1,420	672	--	748	4,685	1,126	--	3,559
obesity	1,164	161	981	159	24,678	67	24,568	16
diabetes type 2	941	638	98	159	6,529	6,135	13	381
GERD	887	753	--	134	2,001	1,059	--	942
heart disease	835	817	4	14	310	299	0	11
poor sleep quality	801	711	--	90	1,000	664	--	336
hypothyroidism	744	680	14	49	849	812	0	37
osteoarthritis	741	741	--	--	197	197	--	--
metabolic syndrome	726	11	715	--	10,656	3	10,653	--
chronic lung disease	527	229	--	298	385	174	--	211
metabolic acidosis	372	2	370	--	N/A	N/A	N/A	N/A
atrial fibrillation	322	242	--	80	406	86	--	320
cancer	266	229	--	37	4,138	3,962	--	176
thrombocytopenia	199	32	167	--	1,098	0	1,098	--
liver disease	198	71	127	--	35	26	9	--
hyponatremia	162	17	145	--	1,323	0	1,323	--
stroke	156	142	--	14	46	24	--	22
achlorhydria	149	0	149	--	720	0	720	--
Parkinson's disease	75	51	--	24	92	36	--	56
monocytopenia	8	0	8	--	10	0	10	--

Table 3 shows the conditions that were not reported in the medical histories but were observed by the AI platform.

This discrepancy reflects on the inconsistency in the delivery of intake data.

In the uMETHOD dataset, 18,262 chronic conditions were reported in medical histories or inferred by the AI platform. Table 3 shows that:

- 3,205 (17.6%) of the chronic conditions were inferred from 2nd and 3rd line medications
- 4,790 (26.2%) of the chronic conditions were inferred from biomarkers and/or vitals

In the NHANES dataset (individuals ages 0 – 79), 96,936 chronic conditions were reported in the medical histories or inferred by the AI platform. Table 3 shows that:

- 14,779 (15.2%) of the chronic conditions were inferred from 2nd and 3rd line medications
- 58,616 (60.5%) of the chronic conditions were inferred from biomarkers and/or vitals

Further investigation is needed to categorize why the chronic conditions listed in Table 3 do not appear in the medical histories received as intake data.

Cognitive Decline and Severe Multimorbidity

Of the 3,876 individuals in the uMETHOD population, 1,912 (49.3%) had cognitive decline.

Counting only the chronic conditions reported in their medical histories:

- 1,847 individuals had SMM, and 1,277 (69.1%) also had cognitive decline
- 1,912 individuals had cognitive decline, and 1,277 (66.8%) also had SMM
- Individuals had an average of 2.48 chronic conditions (SD 2.33, CI 2.41 – 2.55)

Including the chronic conditions observed by the AI platform:

- 3,094 individuals had SMM, and 1,686 (54.5%) also had cognitive decline
- 1,912 individuals had cognitive decline, and 1,686 (88.2%) also had SMM
- Individuals had an average of 4.19 chronic conditions (SD 2.03, CI 4.12 – 4.26)

The AI platform found 1,247 more individuals with SMM (+67.5%), 409 more individuals with both SMM and cognitive decline (+32.0%), and an average of 1.71 more chronic conditions per person (+66.5%).

Pearson's correlation showed a statistically significant, positive linear correlation between the number of chronic conditions an individual has and whether that person has cognitive decline ($r=0.275$, $p < 0.0001$).

Table 4 shows that the percentage of people in the uMETHOD population with cognitive decline increased as their number of concurrent chronic conditions increased. The number of people with more than 8 concurrent chronic conditions was small, so the percentages of people with or without cognitive decline are less meaningful and are not presented here.

Number of chronic conditions	Number of people *without* cognitive decline	Number of people *with* cognitive decline	Percent *with* cognitive decline
0	77	9	10.5%
1	199	59	22.9%
2	280	158	36.1%
3	355	237	40.0%
4	337	292	46.4%
5	272	275	50.3%
6	197	260	56.9%
7	110	207	65.3%
8	49	162	76.8%

Table 4 shows the count of chronic conditions among the uMETHOD population, and for each count, what percentage of this population had cognitive decline.

These same percentages are shown in Figure 1, below.

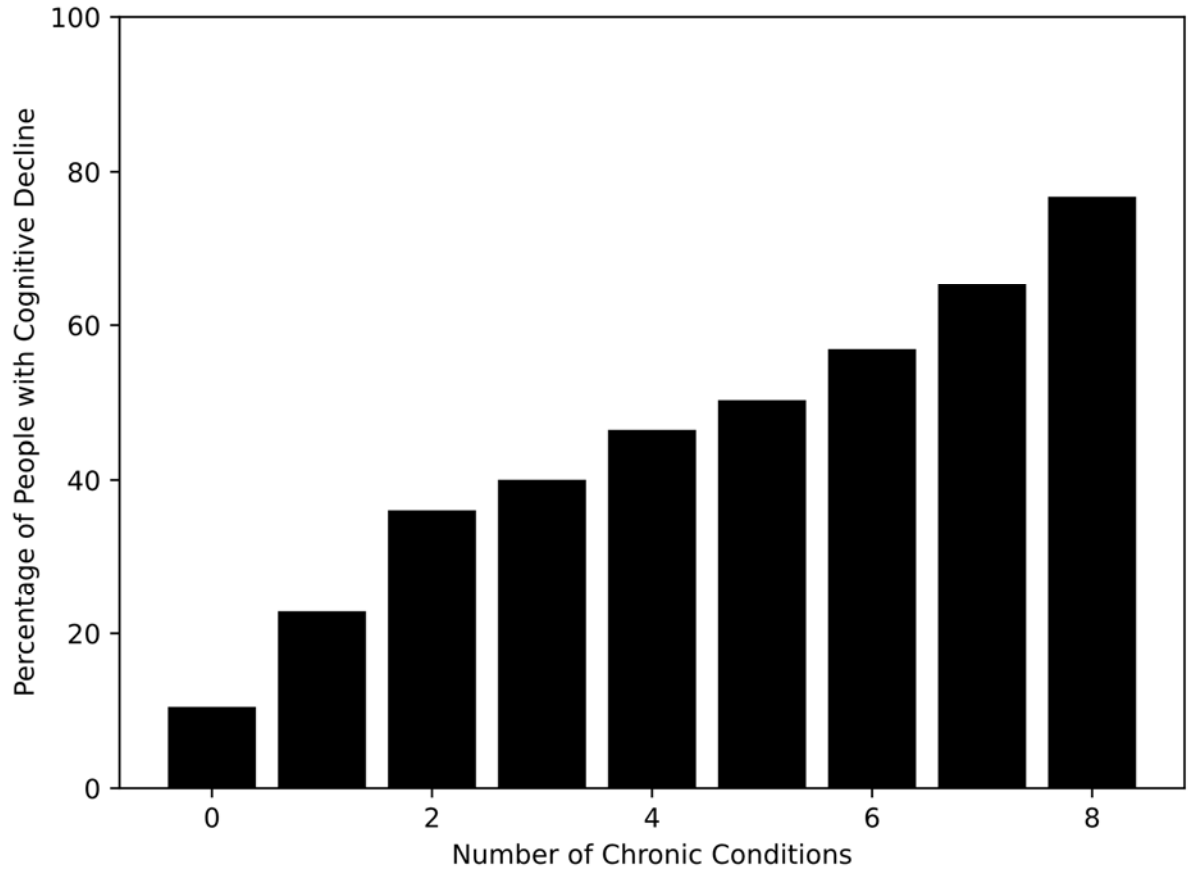

Figure 1 shows the percentage of people in the uMETHOD population with cognitive decline and the number of concurrent chronic conditions that were reported or observed. As the number of chronic conditions increases, the likelihood of cognitive decline increases.

Table 5 shows the number of concurrent chronic conditions, how many people had that many conditions, and the most frequent combination for each number for the uMETHOD dataset. The conditions in these combinations often interact in ways that bring about additional symptoms and complications[19-24]. As above, only the number of chronic conditions from 0 to 8 is shown, as the number of individuals with 9 or more chronic conditions was thin (*e.g.*, 16 people had 13 concurrent chronic conditions).

Number of concurrent chronic conditions	# of people	Most Frequent Combination
0	86	
1	258	chronic kidney disease
2	438	chronic kidney disease, lipid disorders
3	592	chronic kidney disease, hypertension, lipid disorders
4	629	chronic kidney disease, diabetes type 2, hypertension, kidney disease, lipid disorders
5	547	diabetes type 2, hypertension, lipid disorders, metabolic syndrome, obesity
6	457	chronic kidney disease, diabetes type 2, hypertension, lipid disorders, metabolic syndrome, obesity
7	317	chronic kidney disease, depression, diabetes type 2, hypertension, lipid disorders, metabolic syndrome, obesity
8	211	chronic kidney disease, depression, diabetes type 2, hypertension, lipid disorders, metabolic syndrome, obesity, poor sleep quality

Table 5 shows the count of chronic conditions among the uMETHOD population, and for each count, the percentage of this population with cognitive decline.

Age and Multimorbidity

Using the NHANES population, Figure 2 shows the number of chronic conditions increasing with age. There is a statistically significant, positive linear correlation between the number of chronic conditions and age ($r=0.625$, $p < 0.0001$).

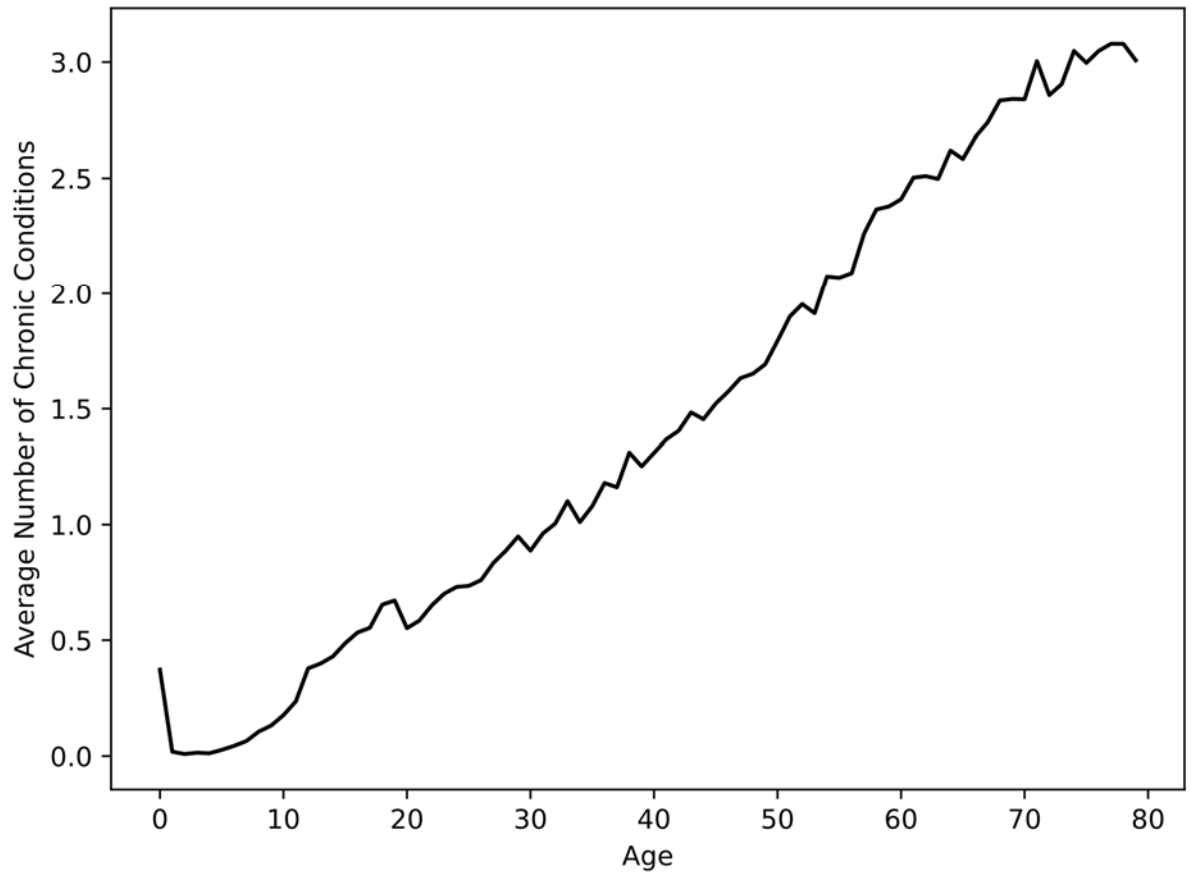

Figure 2 shows the average number of chronic conditions in the NHANES population increasing with age.

Observations

The challenge of managing severe multimorbidity and cognitive decline together is complex:

- SMM is associated with cognitive decline.
- The more concurrent chronic conditions, the greater the likelihood of cognitive decline.
- The number of concurrent chronic conditions increases with age.
- Many concurrent chronic conditions interact with one another.

The AI platform helps reduce the complexity of managing SMM and cognitive decline by:

- Identifying and prioritizing the conditions that are associated with cognitive decline on a per-individual basis. This includes conditions that do not appear in medical histories, but are observed by the AI platform.
- Identifying the medications that an individual is taking that can induce or increase the severity of these conditions.
- Identifying an individual's drug-drug interactions that can increase the risk or severity of these conditions.

Conclusions

Approximately 50% of those with three or more chronic conditions had cognitive decline, and approximately 90% of those with cognitive decline had three or more chronic conditions. Severe multimorbidity and cognitive decline are clearly related, and their treatment needs to proceed hand-in-hand.

Treatment plans for cognitive decline are already multivariable, and must address multidomain SMM as part of their coverage. Neurologists need processes for developing comprehensive care plans that address cognitive decline and comorbidities in concordance, and coordinating care with other physicians simultaneously caring for a given patient. This AI precision-medicine platform generates effective and highly-usable guidelines for identifying and prioritizing chronic conditions, and giving guidance on the total picture: what needs to happen, how, and when.

Disclosures

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with Ethical Guidelines

Following the guidelines set out by "Coded Private Information or Specimens Use in Research" by the Office for Human Research Protection, the work presented here does not qualify as human research. The investigators utilized existing, de-identified data from patients who gave previous informed consent to have their data used in future research, but did not involve the patients in any therapy or intervention.

Data Availability

The data that support the findings of this study are available from uMETHOD Health but restrictions

apply to the availability of these data, which are proprietary company information, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of uMETHOD Health. An earlier version of this paper was published at the July 2020 *Alzheimer's Association International Conference*[27].

Contact Information

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